

**Modification of Age-Related Changes in
Cardiovascular Structure and Function using
Exercise Training**

Dr Helen Caroline Oxenham

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Abstract

Increasing age is associated with substantial changes in cardiovascular structure and function, the cause and permanence of which are unknown. Diastolic function in particular alters appreciably in older adults but non-invasive measurement of cardiac function during diastole has significant limitations. Magnetic resonance imaging with tagging was used to identify changes in three dimensional myocardial strain in older compared to young normal volunteers. This technique identified significantly delayed myocardial relaxation with more myocardial strain persisting in early diastole in older compared to younger individuals. These findings were thought to be attributable to the aging process.

Epidemiological studies and small, non-randomised trials suggest that physical activity might slow cardiovascular aging and improve diastolic function in older adults. A randomised controlled trial was therefore performed to assess whether exercise training could modify age-related changes in older, normal volunteers who had been screened to exclude significant cardiovascular disease. The intervention group underwent six months of supervised exercise training whilst participants in the control group were asked to maintain their pre-trial levels of activity. Measurements made at baseline and after six months included transthoracic echocardiography, cardiac MRI, body composition, blood lipid concentrations, applanation tonometry, quality of life and maximal exercise capacity.

Despite significant increases in exercise capacity in the intervention group, no other significant changes in cardiovascular structure or function, body composition, cholesterol concentration or quality of life were observed when compared to changes seen in the control group.

Six months of exercise training in previously sedentary older adults are insufficient to modify cardiovascular function and structure despite causing marked improvements in exercise capacity. These findings contrast with previously reported non-randomised trials of exercise training in older people. However, they add important, robust information regarding the likely effects of short periods of exercise training on cardiovascular function and structure in older normal adults.

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Declaration

This M.D thesis has been by composed myself from work that was carried out by myself and other members of the Cardiac MRI and Cardiovascular research groups in the University of Auckland. I recruited some of the subjects for the first, comparative study and completed the analysis of tagged MRI images for strain and volume measurements. Myself, Dr Rob Doughty and Professor Norman Sharpe, designed the second, exercise training study. I performed all patient recruitment and screening, including supervision of exercise stress tests and assessments of exercise capacity for the intervention study. Collection of all baseline and end of study data apart from DEXA scans and most of the echocardiograms was performed by myself. Dr Rob Doughty and Dr Richard Meinhold performed the echo and MRI data analysis respectively and Mr Greg Gamble performed the statistical analysis. I collated all data into a database and performed the literature searches required whilst writing this thesis.

I have not submitted any of the research contained in this thesis for any other degree, postgraduate diploma or professional qualification.

I confirm the above declaration to be true and correct.

Signed

Dr Helen Caroline Oxenham

Date10.10.4.....

List of Abbreviations

BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
cm	Centimetres
DEXA	Dual energy x-ray absorptiometry
ECG	Electrocardiogram
IVRT	Isovolumetric relaxation time
LV	Left ventricular
MRI	Magnetic resonance imaging
ms	Milliseconds
SD	Standard deviation
SEM	Standard error of mean

Publications and Presentations

The following chapters have been published or presented prior to submission of this thesis.

- Chapter 1a

Cardiovascular Aging and Heart Failure. Oxenham HC, Sharpe N. European Journal of Heart Failure, Aug 2003 5 (4) 427-434

- Chapter 2

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- Chapter 5

The Effects of Exercise Training on Diastolic Function in Older People: a Randomised Controlled Trial. HC Oxenham, RN Doughty, JC Baldi, KL

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- Chapter 9

Lean Body Mass Rather than Left Ventricular Diastolic Function Predicts

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Chapter 1a

Aging and the cardiovascular system

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Aging and the cardiovascular system

1.1 Introduction

Significant changes have been noted in the structure and function of the cardiovascular system in older people that are considered to be the result of aging. These changes can be regarded as either adaptive or early preclinical disease, but they occur in the absence of clinically manifest disease. In order to study the effects of age on the cardiovascular system, individuals without subclinical or overt disease need to be identified (1). Given the high prevalence of coronary artery disease in this population, careful screening is required and invasive tests such as coronary angiography may be necessary (2).

Evidence regarding human cardiovascular function and structure is generally limited by imaging techniques that are non-invasive and which can be applied serially to measure anatomy and function. Many of the existing disparate findings regarding aging and cardiac function relate to these limitations. The effects of age in isolation can be examined using animal models, although translation of animal data to the human model cannot always be assumed. This chapter reviews the evidence, both in the human and selected animal models, for the changes in cardiovascular structure and function that are associated with the aging process.

1.2 Age-related changes in the arterial wall

Increasing age is associated with increased intimal thickness, vascular smooth muscle hypertrophy, fragmentation of the internal elastic membrane and an increase in the amount of collagen and collagen cross-linking in arterial walls (3, 4). A progressive dilatation and elongation of major arteries as well as an increase in arterial thickening and stiffness accompany these microscopic changes (5). Arterial

stiffening is associated with aging in Western societies even in the absence of demonstrable cardiovascular disease (6, 7). It manifests itself as increased systolic blood pressure (3), widening of the pulse pressure and increased pulse wave velocity (6, 8). These changes create early reflected pressure waves that alter the pressure waveform, lead to an increase in the late systolic pressure peak and contribute to the increased central vascular systolic blood pressure identified in older people (8). Increased arterial stiffness also causes an increase in afterload and end systolic wall stress and these factors may lead to the development of left ventricular hypertrophy.

1.3 Age-related changes in the myocardium

1.3.1 *Left ventricular mass and dimensions*

Although age is a major demographic variable that could affect left ventricular structure, contrasting findings have been reported regarding the relationship between left ventricular mass and age. In the Framingham study, left ventricular mass increased significantly with age in the whole population, but not in the subgroup of normal individuals (9). Other studies have also concluded that, after excluding subjects with coexisting disease, advancing age is not associated with an increase in left ventricular mass (7, 10). In healthy aging individuals, left ventricular structure has been observed to remodel primarily with an increase in relative wall thickness, (ratio of wall thickness to chamber radius) but with little or no increase in overall left ventricular mass (11). This concentric remodeling parallels the age-related stiffening of the arterial tree, whilst hypertension commonly results in concentric hypertrophy of the myocardium with an increase in left ventricular mass. Thus, the increase in left ventricular mass that is often reported to accompany increasing age is likely to be predominantly a function of extra-myocardial influences rather than an intrinsic myocardial aging process.

The relationships between age, left ventricular wall thickness and left ventricular volumes are also controversial. Some studies report small reductions (11) and others small increases (12) in left ventricular volumes or left ventricular wall thickness (7, 11) with advancing age. Errors in wall thickness measurements and derived calculations of left ventricular mass may explain this disparity (13). Significant changes in left ventricular outflow tract geometry occur in older people (13), resulting in a narrowing of the angle between the aorta and the interventricular septum. This changes the position of the interventricular septum relative to the chest wall and leads to systematic errors in echocardiographic M-mode measurements across the left ventricle. In addition, up to 10% of people over the age of 65 years are noted to have a “septal bulge”, or widening of the proximal interventricular septum on echocardiography (13), which may also be a result of the anatomical alterations described above.

1.3.2 *Histology*

Histopathological data tend to support the finding that increasing age does not result in an increase in left ventricular mass. Approximately 35% of the total number of myocytes in the ventricles is lost between the age of 30 and 70 years (14). The cause of this cell death is unknown, but a reduction in capillary density has been noted to occur with increasing age and may lead to ischaemic injury (10). Perhaps as a compensatory mechanism to account for the cell loss, the volume of the remaining myocytes increases (7, 14). Whether aging in humans is associated with significant changes in myocardial collagen content remains controversial (12). However, the expansion of the myocyte and non-myocyte compartments of the myocardium occurs in such a way that the proportions of these two structural constituents remain

unchanged (14) and no overall change in myocardial volume with increasing age is observed.

1.3.3 *Molecular changes*

Important cellular and molecular alterations underlie the functional abnormalities of the aging myocardium and may represent adaptive compensatory phenomena that result in energy preservation. These alterations include a defect in sarcoplasmic reticulum Ca^{2+} ATPase pump activity, which controls the rate of calcium re-uptake into the sarcoplasmic reticulum during relaxation (15). There is also a significant reduction in cardiac sarcoplasmic reticulum Ca^{2+} ATPase protein concentration (16). Experimental evidence suggests that these changes cause a significant prolongation of isovolumetric relaxation (17). Changes in myosin iso-enzyme type from one with high, (V1) to one with low, (V3) ATPase activity (12, 14), have also been documented in senescent rats. Prolonged contraction and a reduced velocity of myocardial fiber relengthening accompany this change (14), which has not been observed in the human myocardium.

1.3.4 *Left ventricular systolic function*

Left ventricular systolic function remains relatively well preserved and there are no significant changes in left ventricular ejection fraction, cardiac output or stroke volume at rest (18) with increasing age in men or women (5, 12, 19). Recently, we used cardiac magnetic resonance imaging with tagging to assess myocardial function in healthy older adults and were also able to confirm maintenance of normal ejection fraction and stroke volume with increasing age (20). This study did, however, show changes in the material motion of the myocardium in older subjects. These changes were consistent with the 20% reduction in longitudinal shortening and 18% increase

in short axis shortening between the ages of 18 and 70 years, identified previously in echocardiographic studies (21). Changes in the material motion of the left ventricle that accompany increasing age may be due to the larger mass to end diastolic volume ratio that has been identified in older people but the significance of these changes is uncertain.

1.3.5 *Left ventricular diastolic function*

In contrast to left ventricular systolic function, advancing age is associated with striking alterations in left ventricular diastolic function (22, 23). In humans, cardiac catheterisation is the standard technique for direct measurement of diastolic function using left ventricular filling pressure to assess the rate of left ventricular relaxation. Unfortunately, this technique is invasive and therefore has limited applications. Doppler echocardiography is now accepted as an excellent non-invasive method with which to assess left ventricular diastolic function by measuring blood flow from the left atrium to the left ventricle. Despite significant limitations with this technique such as heart rate (24) and load dependence (25), the parameters obtained provide useful information regarding changes in diastolic function with aging.

Transmitral flow

Several large studies have confirmed a significant association between early, E, and late, A, transmitral flow velocities and age (23, 26). Changes in these indices occur gradually and progressively (26, 27) and consist of a reduction in early left ventricular filling of approximately 50% (28, 29), together with a 40% increase in late left ventricular filling between 30 and 70 years of age (30). These findings have been shown to be independent of cardiovascular disease (29) or central haemodynamic parameters (22), are accompanied by a prolongation of the

deceleration time of the E wave (12, 31), an increase in left atrial size (23) and are present in more than 85% of healthy people over the age of 70 years (27). Doppler indices are reflective of flow patterns and are not synonymous with function; therefore, it is questionable whether age-associated changes in diastolic function signify pathology in an individual subject (26). However, it is generally accepted that mitral inflow pattern change with age is likely to be an effect of aging alone.

Myocardial diastolic velocities

Tissue Doppler imaging measures low amplitude myocardial velocities and can provide an assessment of the rate of longitudinal dimension or volume change during diastole (32). It has been shown to be less load and heart rate dependent than transmitral flow velocities and can therefore provide additional information regarding the diastolic properties of the left ventricle. A significant fall in the ratio of early to late myocardial velocities, (E'/A') with increasing age is seen (33, 34, 35) and although reversal of the transmitral E/A ratio occurs in the seventh decade, reversal of the E'/A' ratio occurs earlier, in the fifth decade (32).

Left ventricular compliance

Compliance is a term that is used to describe the deformability of a substance. It has long been suggested that aging is accompanied by a stiffening of the left ventricle in normal people, yet there is little direct evidence to support this theory. Reduced left ventricular compliance associated with increasing age was identified in an animal study using invasive, simultaneous monitoring of pressure and volume (12). Passive compliance has been measured in rats and, in the absence of hypertension or other cardiovascular disease, does not appear to change with age (36). Direct evidence that age related increases in left ventricular stiffness occur in humans has been provided

by a study that measured left ventricular pressure-volume relationships in elderly people with chest pain who were being assessed by coronary angiography (19). Increased left ventricular diastolic stiffness correlated significantly and increased with advancing age and these findings were confirmed in another similar study (37).

Myocardial relaxation

Myocardial relaxation is a complex process that depends upon early diastolic release of elastic energy that has accumulated during systole (38). It can be measured indirectly by assessing the time constant of left ventricular pressure decay during isovolumetric relaxation, τ (39-41), or non-invasively, by measuring isovolumetric relaxation time and transmitral flow velocities using Doppler echocardiography (29). Unfortunately, the techniques used to measure myocardial relaxation yield conflicting results regarding the relationship between myocardial relaxation and aging (12, 40, 42). In addition, they are unable to directly assess the complex and non-uniform (43), three-dimensional untwisting motion that occurs during myocardial relaxation and diastole. However, animal studies and research using tagged magnetic resonance imaging have been able to identify a prolongation of myocardial relaxation in mammalian hearts with advancing age (20).

1.4 Conclusions

The aging process itself is a major factor that contributes to changes seen in the cardiovascular system in older people. Stiffening of the arterial tree is responsible for alterations in afterload and left ventricular geometry and although resting left ventricular systolic function is unchanged, left ventricular diastolic function alters substantially. These diastolic abnormalities are due to changes in myocardial "make up" at a molecular level and include reduced compliance and prolonged relaxation.

1.4.1 *Clinical significance*

The age-related changes described above may represent physiological impairment or one end of the spectrum of clinical disease. Although they are very common, their significance with respect to the subsequent development of cardiac diseases such as heart failure is uncertain. However, age-related changes are likely to lower the threshold for the clinical manifestation of cardiac disease such as heart failure, which has a high prevalence in older adults (44). A substantial proportion of these cases are found to have normal or near normal left ventricular systolic function and the cause of heart failure in these individuals is thought to be diastolic impairment. A significant reduction in early left ventricular filling is noted in the majority of older people and this leaves the left ventricle less distended and results in a failure of the Frank Starling mechanism. This, together with the age associated reduction in left ventricular compliance means that, during episodes of myocardial ischaemia or uncontrolled hypertension, left atrial and left ventricular end diastolic pressure increase and lead to pulmonary congestion and oedema more readily than in younger people. Thus, age-related changes in the function of the cardiovascular system, together with the high prevalence of hypertension and coronary artery disease combine to greatly reduce cardiovascular reserve and significantly increase the risk of heart failure in older adults (45).

Less marked alterations in cardiovascular function and structure are observed in master athletes and several studies have documented partial reversibility of some age-related changes following exercise training in older people. Animal studies provide further evidence that the “aging” of the cardiovascular system may be modified by physical activity or genetic modification. However, further research is required to evaluate the permanence and significance of these common physiological

and structural age- related phenomena so that methods to alter or delay this aging process can be identified.

Table 1 Chapter 1a

Age-associated changes in cardiovascular function and their clinical consequences

	Change associated with aging	Clinical consequences
Arterial wall	<ul style="list-style-type: none"> • Increased thickness • Reduced compliance 	<ul style="list-style-type: none"> • Increased systolic blood pressure, afterload, and pulse wave velocity • Widening of pulse pressure
Myocardium	<ul style="list-style-type: none"> • Loss of myocytes • Increased ratio of left ventricular wall thickness to chamber size 	<ul style="list-style-type: none"> • Reduced left ventricular compliance
Cellular changes	<ul style="list-style-type: none"> • Reduced sarcoplasmic reticulum Ca^{2+} ATPase protein concentration • Reduced reuptake of Ca^{2+} into sarcoplasmic reticulum 	<ul style="list-style-type: none"> • Prolongation of myocardial relaxation • Increased isovolumetric relaxation time
Systolic function	<ul style="list-style-type: none"> • Preserved 	
Diastolic function	<ul style="list-style-type: none"> • Reduced early diastolic filling • Increased late diastolic filling • Reduced myocardial diastolic velocities 	<ul style="list-style-type: none"> • Reduced E velocity • Prolonged E deceleration time • Increased A velocity • Reduced E' and E'/A'

Chapter 1b

Aging and the Cardiovascular Response to Exercise

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Aging and the Cardiovascular Response to Exercise

1.5 Introduction

Aging in healthy adults causes changes in the cardiovascular system and in skeletal muscle that can affect exercise tolerance as well as everyday functional ability (12, 46). Age-related cardiovascular alterations in some ways parallel the changes that may occur with deconditioning and which also result in an altered response to exercise (47). Several factors contribute to the altered response to exercise in older people including health status and life-style as well as a genetic component (48). Training in older adults can improve exercise tolerance but the mechanisms by which this occurs remain unclear. Evidence regarding aging and the responses of the body to exercise training are discussed below.

1.6 Exercise capacity declines with aging

The physiological response to dynamic exercise is complex and involves several organ systems, each of which is a potential limiting step for the transport of oxygen to and uptake by the exercising muscles. Oxygen delivery to the muscles by the circulation has been considered one of the most important limiting factors in exercise capacity (49). Alternatively, exercise capacity may be limited at the cellular level when oxygen utilization by the muscles reaches a maximum (50). Oxygen uptake, VO_2 , is a measure of the ability of the heart and lungs to supply oxygen to the working muscles and the capacity of those muscles for aerobic metabolism (46). VO_2 increases linearly with intensity of exercise (51) and $\text{VO}_{2\text{max}}$ is the greatest amount of oxygen a person can use while performing dynamic exercise involving a large muscle mass (52). In conventional exercise testing this is a common measurement for evaluating the capacity of the cardiovascular system and it is often used as a reflection of maximum cardiac output (49). $\text{VO}_{2\text{max}}$ is significantly related to age,

gender, exercise habits, heredity and cardiovascular clinical status (52). A progressive decline in VO_2max generally occurs with advancing age, starting between the ages of twenty and thirty years and falling by approximately 10% per decade, (Figure 1, Chapter 1b), (18, 46, 53, 54). The decline is present in sedentary populations even when adjusted for weight (12) but is less marked, though still significant (54) when normalized to an index of muscle mass (12) and is seen in longitudinal (55) as well as cross sectional aging studies (5). Is this documented decline in exercise capacity caused by aging per se, a sedentary lifestyle per se, changes in body composition or an interaction between aging and lifestyle?

1.7 Causes of the decline in exercise capacity with aging

The relative contributions of the possible underlying mechanisms for the reduction in exercise capacity with advancing age remain unclear. Maximum oxygen consumption is equal to maximum cardiac output multiplied by maximum arteriovenous oxygen difference. Thus, two opposing theories have been proposed to explain the reduction in exercise capacity seen with aging: a central cardiac limitation or a peripheral limitation involving muscle mass and metabolism. Central cardiovascular factors that may influence VO_2max , through failure to divert enough blood to the muscles, include a reduced cardiac output, reduced stroke volume and reduced maximum heart rate during exercise in older people (12). Alternatively, peripheral limitations in older people include a larger mass of adipose tissue (54, 56) and smaller muscle mass, or a diminished capacity for the muscles to utilize oxygen during exercise. The various components that may lead to a reduced exercise capacity in older persons will be discussed further.

1.7.1 *Peripheral oxygen use: skeletal muscle mass*

A reduction in muscle mass and strength begins in middle age in healthy people even when body weight is preserved and this is due to loss of muscle fibres rather than a reduction in fibre size (5, 46, 57). It has been suggested that as much as 50% of the age-associated decline in VO_2max can be attributed to a reduction in muscle mass in untrained men as they age (58). In patients with congestive heart failure, skeletal muscle mass, rather than total body weight independently predicts VO_2max during exercise and this important determinant of exercise capacity is thought to be independent of central haemodynamics, neurohormonal activation, gender and age (59). The value of VO_2max in defining functional status can therefore be enhanced by correcting absolute VO_2max for skeletal muscle mass rather than body weight, especially in older people and in women (59). However, in a study that examined exercise capacity in five middle aged men on two occasions separated by 30 years, there was a significant fall in VO_2max and a substantial increase in percent body fat but no change in fat free mass over the time period (56).

1.7.2 *Peripheral oxygen use - Muscle oxidative capacity*

Some studies suggest that aging does not alter muscle energy metabolism (12), although other evidence reports myofibrillar disorder and changes in mitochondrial structure and distribution that lead to a reduction in the oxidative capacity per gram of muscle in sedentary older subjects (54). There may also be an inefficient redistribution of blood flow to working muscles and lower capillary density in the elderly, which also causes a reduction in oxygen extraction and use per unit of muscle (12, 54). A decline in maximum arteriovenous oxygen difference was thought to account for the entire decrease in cardiovascular capacity in a longitudinal study

spanning 30 years (56) and it is possible that impaired peripheral oxygen extraction may be the primary mechanism by which exercise capacity decreases in older people.

1.7.3 Central cardiac factors

Variations in findings regarding changes in central cardiac factors with exercise are evident from the numerous studies in the literature that cite conflicting results. The presence of occult disease exaggerates the age-associated trends for left ventricular end diastolic dilatation and causes larger end systolic volumes and reduced ejection fractions compared to healthy age-matched older people (12). Co-existing disease must therefore be excluded by careful screening of study participants. In addition, many studies have too few subjects to identify small changes in left ventricular volume or mass when measured using echocardiography. Both gender (5) and the level of physical activity have significant effects on left ventricular end diastolic volume, stroke volume and cardiac output during exercise, so that it is important to match for these factors too when assessing cardiac reserve in older populations (54). Despite these limitations, decreases in maximum heart rate and stroke volume at peak exercise have been documented in longitudinal studies of aging (60) and both may contribute to a reduced cardiac output and $\text{VO}_{2\text{max}}$ in older subjects.

Cardiac output

There have been few large studies measuring cardiac output during exercise in older populations. Most studies conclude that cardiac output during exercise tends to decrease with advancing age (47, 61) by approximately 1.2L/min per decade and is most noticeable in the eighth decade (12, 48). A reduction in cardiac output partly reflects decreased demand and reduced skeletal muscle mass (28) and this is thought

to be a major factor responsible for the reduction in VO_2max in elderly mammals (48).

Maximum heart rate

Although resting heart rate shows little alteration with age (57), maximum heart rate during exercise decreases progressively from the age of ten, by approximately one beat per minute per advancing year (5, 18, 46, 48). The mechanism for the reduction in maximum heart rate is unknown (48), but it is not attributable to disease and is not affected by physical conditioning of any duration or intensity (12, 58, 62, 63).

However, a reduced maximal heart rate is felt to contribute little overall to the fall in VO_2max with increasing age (55). In a longitudinal study of endurance athletes over a 21 year time span, VO_2max fell by 20% and was accompanied by a 9% reduction in heart rate but there was no correlation between the maximum heart rate difference and VO_2max change (12).

Stroke volume

The role of a reduced maximal stroke volume in explaining the age-associated difference in VO_2max is controversial, but it is thought to have a greater impact than a reduced maximum heart rate (56). Stroke volume index at peak exercise is reduced in older individuals (5, 47, 64). This is the consequence of age-related changes in the cardiovascular system such as reduced inotropic and chronotropic β adrenergic stimulation, increased vascular stiffness and aortic impedance, reduced ejection fraction and impaired left ventricular diastolic function (65). When matched for maximal work capacity, stroke volume at maximal exercise increases due to a substantial increase in end diastolic volume in older compared to young men, (28, 47, 64). This change in left ventricular volume partially offsets the age-related

decrease in maximal heart rate but because end systolic volume index fails to decrease adequately, stroke volume remains significantly reduced compared to younger men (66).

β adrenergic responsiveness

Evidence in humans and animals suggests that the effectiveness of β adrenergic modulation on myocardial contractility, heart rate and vascular tone declines with advancing age (64, 65) and is thus likely to account for some of the altered responses of the cardiovascular system to exercise in older people (67). Whilst both β adrenergic receptor density and the ratio of β_1 to β_2 receptors do not change with aging (68), senescent myocytes show a decreased cardiac responsiveness to β adrenergic stimulation (17). This reduced β adrenergic responsiveness leads to a failure of the end systolic volume to reduce on exercise (5, 12) and as the ratio of end systolic volume to systolic blood pressure is a crude index of myocardial contractility, this also reduces with exercise as a function of age (12).

Ejection fraction

With advancing age, there is a reduced ability to increase ejection fraction from resting levels during exercise so that ejection fraction at peak exercise is reduced in older individuals (47, 64). Port et al (60) used radionuclide ventriculography to assess left ventricular ejection fraction and left ventricular volumes at rest and during exercise in normal volunteers. A striking reduction in ejection fraction at peak exercise was documented in older subjects at the same workloads as younger subjects although the presence of occult coronary artery disease in older subjects may have been responsible for some of this reduction. Increased afterload, reduced aortic compliance (47) and increased left ventricular wall stress may singularly or in

combination compromise the ejection of blood during exercise, leading to a diminished increase in ejection fraction in older people (64). Additional information that supports this theory comes from a study in which cardiovascular function on exercise was measured following vasodilator treatment (69). Arterial stiffness and early arterial pressure wave reflection decreased significantly following administration of nitroprusside, as did systemic vascular resistance, augmentation index, end diastolic volume and end systolic volume. These changes resulted in an increased ejection fraction at rest and during exercise (69). Thus, in healthy older people, increased afterload prevents the left ventricle from emptying as completely as in the young (69) so that stroke volume elicited by the Frank Starling mechanism during exercise is limited.

Central cardiac factors - Summary

In older healthy men, compensation for age-related cardiovascular changes is accomplished through maintaining stroke volume by increasing left ventricular end diastolic volume, (Table 1, Chapter 1b), (18, 63). Exercise induced increases in stroke volume and cardiac output therefore depend on augmented cardiac filling with greater reliance on the Frank Starling mechanism in older compared to young people. The Frank Starling mechanism is however, less effective in the elderly due to reduced maximal contraction, reduced augmentation of contractility (5) and increased afterload.

Central haemodynamic changes thought to occur in old compared to young normal subjects during exercise

Lower maximum heart rate

Smaller reductions in end systolic volume

Smaller increases in ejection fraction and stroke volume

Greater increases in end diastolic volume

1.8 Diastolic function and exercise capacity

1.8.1 *The consequences of changes in diastolic function during exercise*

An important mechanism by which age may influence exercise capacity through its impact on cardiac function is the alteration in left ventricular diastolic performance that is known to occur with increasing age (70, 71). Aging is associated with marked alterations of diastolic filling both at rest and during isometric (72) and aerobic exercise (70). During exercise, the duration of diastole is shortened dramatically secondary to tachycardia. The consequence of a reduced left ventricular filling period coupled with age associated diastolic impairment may result in filling rates on exertion that are too low to achieve adequate increases in cardiac output during exercise (51) and thus be the critical factor limiting aerobic performance (71).

1.8.2 *Relationships between diastolic function and exercise capacity*

Recent studies suggest that much of the variation in exercise performance among individuals and between groups is due to differences in left ventricular diastolic filling in normal people (51, 70, 73). Invasive monitoring of left ventricular pressure

in people with coronary artery disease has identified that measures of diastolic rather than systolic performance correlate significantly with VO_2max (74). Resting peak filling rate, E and E/A ratios have both been shown to be powerful independent predictors of VO_2max in the elderly (70). In addition, following calcium channel blockade, left ventricular filling and exercise capacity are both increased in older sedentary and hypertensive men (50). These findings would suggest that changes in diastolic filling do indeed limit exercise capacity in older people (51).

1.8.3 *Augmentation of left ventricular filling during exercise*

In order to maintain cardiac output during exercise left ventricular filling needs to be augmented significantly and to a greater extent than do ejection rates during systole (51, 73). Exercise is associated with a progressive acceleration of isovolumetric relaxation (74) and animal studies have identified negative intraventricular pressure in early diastole during exercise. This is thought to be due to increased elastic recoil, which creates more effective left ventricular suction and augments left ventricular diastolic filling during exercise. Increased elastic recoil or augmented cardiomyocyte relaxation occurs as a result of increased calcium reuptake secondary to β adrenergic stimulation during exercise (73). β blockade dampens this suction effect and has been shown to eliminate age-related differences in diastolic filling between young and old men. Thus, some of the reduced left ventricular filling identified in older men on exercise is due to a reduced suction effect and this in turn is due to reduced β -adrenergic responsiveness (65). Pulmonary capillary wedge pressure has been shown to increase slightly on exercise in older people and in itself would increase the left ventricular pressure gradient, tending to increase left ventricular filling. However, the relative contribution of the above mechanisms with respect to left ventricular filling

is uncertain (70) and factors that contribute to increased left ventricular filling are different to those that enhance cardiac output (73).

1.9 Cardiovascular function in athletes

Master athletes have reduced subcutaneous fat, increased muscle mass, increased peripheral oxygen utilisation and a VO_2max nearly twice that of sedentary age-matched people (12). Most, but not all studies identify greater left ventricular mass in athletes compared to sedentary controls. Milliken et al (75) used cardiac MRI to identify significant increases in left ventricular mass in competitive athletes and suggested that some of the previous confusion regarding changes in myocardial mass in athletes arose due to lack of precision when measuring left ventricular mass using echocardiography (75). In addition, left ventricular mass was found to correlate strongly with VO_2max , ($r = 0.8$) and this supports the assumption that it is training that causes the increase in left ventricular mass in this group.

1.9.1 Mechanisms by which exercise capacity is maintained in athletes

Both enhanced myocardial contractility and augmented diastolic filling appear to contribute to the enhanced VO_2max that is observed in athletes. This increased exercise capacity is also associated with an increased capacity for the cardiovascular system to deliver oxygen and of the muscles to use that oxygen (52).

Myocardial contractility

Several studies have shown athletes to have higher ejection fractions; smaller left ventricular systolic volumes and larger left ventricular end diastolic volumes and thus stroke volumes (54) than sedentary subjects during exercise (76-78). These data

suggest that increased exercise cardiac output is achieved in athletes through amplification of the length-tension relationship of cardiac muscle. This improved myocardial contractility may be mediated through enhanced sensitivity to β -adrenergic stimulation, but the exact mechanism is unclear. Longitudinal studies examining the effect of aging on the cardiovascular system over 33 years report no increase in blood pressure in endurance trained men (79). The absence of an increasing afterload with advancing age may also help athletes to maintain left ventricular ejection fraction during exercise.

Diastolic function

Many studies have identified increased left ventricular mass in athletes (51, 73, 76, 80, 81). However, unlike left ventricular hypertrophy caused by pressure overload, the physiological hypertrophy associated with exercise training does not appear to impair early left ventricular diastolic filling (73, 81). Some authors suggest that the age-associated reduction in early left ventricular filling is less pronounced in endurance-trained athletes who have higher E/A ratios than sedentary peers (78, 82, 83). Thus, physical activity may modify cardiac structure and diminish the expected age related alterations in diastolic left ventricular filling. However, not all authors have identified significant differences in left ventricular diastolic flow velocities compared to non-athletes. In addition, exercise training generally results in a reduction in resting heart rate and this may also influence Doppler echocardiographic measures of transmitral flow. It is therefore difficult to separate the effects of a reduced heart rate from training related changes in diastolic function. E/A ratio has been identified as a major predictor of VO_2max (51) and therefore training induced facilitation of left ventricular filling has been proposed as the mechanism by which exercise capacity is increased in endurance athletes compared to age-matched

untrained individuals. However, both an increase in total blood volume, of approximately 7% (73), as well as a reduction in peripheral resistance (84) and increased peripheral venous tone occur following exercise training. These changes enhance venous return, increase end diastolic wall stress and parallel improvements in exercise performance (66, 73). Thus, the increase in early diastolic filling identified in athletes may merely result from the changes in preload and afterload detailed above (80). Diastolic function can now be measured using tissue Doppler imaging, which is less sensitive to heart rate or loading conditions than conventional Doppler estimates of diastolic function. Myocardial velocity gradients were measured in the posterior wall of the left ventricle in athletes and sedentary subjects using tissue Doppler imaging (85). Although no significant differences in measures of left ventricular systolic performance were seen in this study, athletes did have significantly higher diastolic indices than sedentary normal individuals and the magnitude of the difference was independent of heart rate, blood pressure and left ventricular dimensions.

1.10 Exercise training in older people

Physical inactivity probably contributes to the reduction in both exercise capacity and peak cardiac output that occurs with increasing age because aerobic exercise training can induce changes in the cardiovascular system that partially reverse the age related decline in exercise capacity (65, 86). The mechanisms by which exercise training improves exercise capacity in older people will be examined further.

1.10.1 *Improvements in exercise capacity following exercise training*

Although earlier studies did not show improvements in VO_2max in older people, it is now clear that vigorous exercise training can enhance VO_2max both in older men and women (87). In addition, the degree to which the cardiovascular system can respond to endurance exercise training in older age appears to be maintained in individuals over 70 years of age in whom improvements in VO_2max of 10 to 20% have been documented; a similar amount to that observed in young subjects following training (63, 87). Responses to exercise training have greater variability in older subjects (48) but the effects of exercise training on left ventricular performance and cardiovascular function do not depend on initial levels of fitness (86). However, as individuals age, the degree to which exercise training can reverse the decline in VO_2max falls (55, 58, 63) and whilst the percentage change in VO_2max following exercise training is similar in old and young subjects, absolute values are smaller in older populations (87). In a meta-analysis of age-associated changes in VO_2max , absolute and relative rates of decline with age were seen to be the same in sedentary and endurance-trained individuals (88). This does not concur with previously held views that VO_2max decline with age is smaller in exercise trained compared to sedentary groups even though absolute levels of VO_2max at any age are higher in active populations.

It is commonly stated that half of the improvement in VO_2max with exercise training in young people is due to increased cardiac output and half is due to a widening of the arteriovenous oxygen difference. Following exercise training in older people, is the improvement in exercise capacity due to an increase in cardiac output, an increase in arteriovenous oxygen difference or both?

1.10.2 *Central cardiovascular adaptations to exercise training*

Reduced maximal cardiac output has been shown to account for up to 80% of the age-related differences in VO_2max between young and old trained individuals but only 40% of the difference between young and old untrained individuals (47, 54). As maximum heart rate does not seem to change much with exercise training, it can be assumed that any central cardiac adaptations that follow exercise training are brought about by changes in stroke volume (52).

Effect of exercise training on stroke volume

Numerous investigators have studied the morphological changes that the heart undergoes following training, many using echocardiography to assess changes in cardiac dimensions. However, there are few randomised, controlled trials that examine the effects of exercise training on cardiac dimensions in older people (46, 67). One randomised, controlled trial of exercise training in older women suggested that improved exercise capacity was due in part to increases in left ventricular end diastolic volume following exercise training (89). Unfortunately, many non-randomised exercise training studies reporting changes in cardiac size after brief periods of exercise training have not described the blinding techniques used in echo measurements and any effect on systolic and diastolic volumes may be more apparent when determined during exercise rather than at rest (90). Therefore, convincing data regarding changes in left ventricular volumes following exercise training remain limited. Training is however thought to increase stroke volume by 20% or more, partly due to increased plasma volume and increased peripheral venous tone, partly due to reduced afterload and partly due to increased myocardial

contractility (91). Therefore, improvements in VO_2max in older people may be related to a larger maximal cardiac output secondary to larger stroke volumes (76).

Effects of exercise training on ejection fraction

Studies have confirmed a reduction in 24 hour and resting blood pressure following exercise training and exercise is thought to reduce systolic blood pressure by, on average, 11mmHg and diastolic blood pressure by approximately 6 mmHg (92). Indeed the evidence supporting the anti-hypertensive effect of exercise has induced the World Hypertension League to recommend physical training as a non-pharmacological measure to treat mild hypertension. As fitness increases, there is an improved ability of the left ventricle to empty due to reduced arterial stiffness (6) and exercise training has been shown to improve ejection fraction at peak exercise even in studies showing increases in exercise systolic blood pressure (64). Myocardial contractility may also play an important role in improving exercise ejection fraction. Evidence for this comes from a study that documented improvements in left ventricular systolic performance in response to an afterload stress in older healthy men following exercise training (61). This adaptation is mediated in part by an augmented contractile state; however, enhanced left ventricular filling and left ventricular hypertrophy secondary to exercise training may also contribute (61).

Effects of exercise training on myocardial contractility

Although Stratton et al (24) suggested that improvements in cardiac function with training were probably not related to increased β -adrenergic responsiveness (67, 86), other authors have suggested that an adaptive increase in cardiac responses to catecholamines is one of the mechanisms by which exercise training may improve left ventricular systolic and diastolic performance (65). Experiments with rats

confirm shorter contraction duration after exercise (36) but little research has been performed to quantify the effects of exercise on ventricular dynamics in humans. It has been suggested that the enhanced inotropic response to catecholamines causes a reduction in end diastolic volume at the same wall stress and this is consistent with improved contractile function. These adaptive increases in left ventricular systolic function and subsequent cardiac output and stroke volume at peak exercise are almost abolished after β -adrenergic blockade (69). This increased inotropic response is in contrast to the chronotropic response that does not change significantly with exercise training. The mechanism underlying the absence of an increase in maximal exercise heart rate may relate to a selective reduction in β -adrenoceptors in the right atrium in response to training (65, 93).

Gender plays a significant role in the physiological adaptations to exercise training. In postmenopausal women, adaptations in skeletal muscle are thought to be responsible for most of the increase in exercise capacity, as evidenced by an increased arterio-venous oxygen difference, without a significant increase in cardiac output or stroke volume (3, 54, 76). However, in older men a large proportion of the improvements in exercise capacity are attributed to increases in cardiac output and stroke volume during exercise (94). Women seem also to develop no significant physiological left ventricular hypertrophy or increase in β -adrenergic mediated cardiac adaptations to exercise. In contrast, physical conditioning of sedentary older men results in significant increases in exercise capacity, peak work rate, stroke volume index and cardiac index, mediated in part by an increase in inotropic response to β adrenergic stimulation, and detraining results in corresponding decreases in the same parameters (86, 89).

1.10.3 *Peripheral adaptations to exercise training*

Parkkari et al (95) found that playing golf three times per week increased exercise tolerance and reduced weight and percentage fat in middle aged men. Other beneficial effects of exercise training that have been reported include improved insulin sensitivity, improved control of diabetes and reduced obesity (91). However, the pattern of beneficial cardiovascular effects attributed to the conditioned state does not necessarily depend on changes in body composition (56, 86).

Effects of training on skeletal muscle function and structure

Whilst skeletal muscle oxidative capacity and capillary density are lower in older sedentary subjects, they are not different in old versus young, trained individuals (54) and this suggests that training can improve oxidative capacity and capillary density. Improvements in peripheral oxygen consumption following exercise training have been identified in older women and men (76) but not by all authors (89). Strength training does not halt the underlying loss of muscle fibres secondary to the aging process and does not seem to improve VO_2max in older people (87) but the improvements in strength are equivalent to 15 to 20 years rejuvenation (46).

1.10.4 *Effects of exercise training on left ventricular diastolic function*

Perhaps the most obvious manifestation of exercise training is a decrease in resting heart rate. Among other benefits, the longer diastolic period enables improved myocardial perfusion. However, by altering heart rate and cardiac function time intervals, exercise training may alter the natural progression of diastolic dysfunction that occurs with advancing age. Training also influences myocardial geometry and cardiomyocyte biochemistry (73) and enhanced ventricular relaxation may occur due

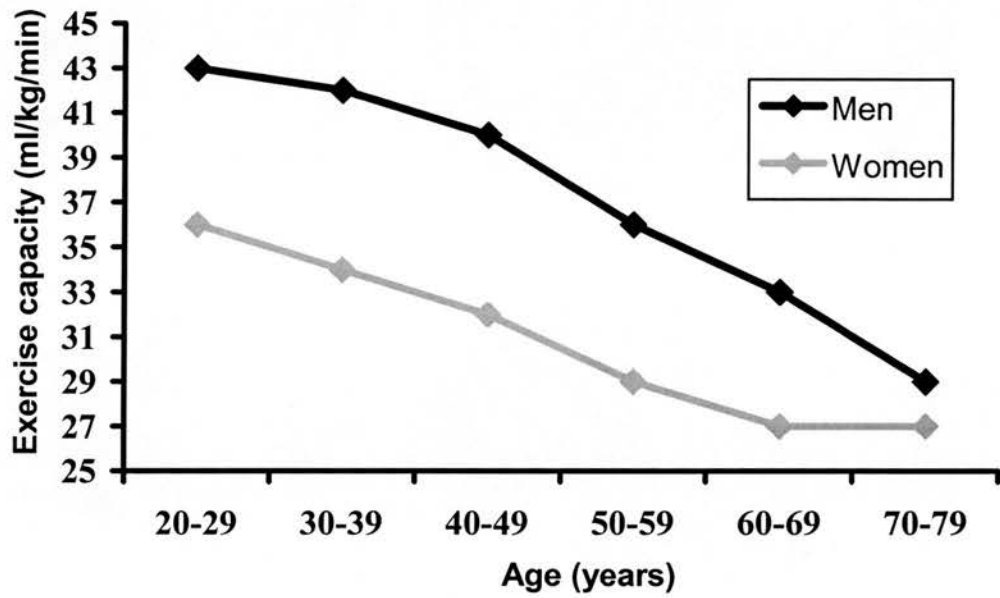
to an increased calcium uptake by the sarcoplasmic reticulum. This has been shown to occur in animal studies where exercise training has resulted in improvements in most of the metabolic abnormalities that are thought to cause age-related alterations in diastolic function (36, 70). Cross sectional studies in humans have suggested that exercise training may improve diastolic filling whereas longitudinal training studies in the young have shown no change. Levy et al (70) did show improvements in peak left ventricular filling rate at rest and during exercise after six months of exercise training, suggesting that endurance training can enhance early diastolic filling at rest and during exercise in both old and young men. Training also reduced the atrial contribution of left ventricular filling in older people and the increase in exercise capacity following exercise training in older men appears to be related to this altered diastolic function. Belardinelli et al demonstrated that short-term physical training could improve exercise capacity and was associated with an increase in early diastolic filling at rest and during exercise in patients with heart failure (96). In another study, neither an increase in plasma volume secondary to training (71), nor a change in the responsiveness to β -adrenergic stimulation were thought to be the cause of the training induced improvements in diastolic function in older people (97). It is important to note, however, that measurements of diastolic function using transmitral Doppler inflow velocities may have been influenced by changes in heart rate and blood pressure that occur as a consequence of exercise training.

1.11 Conclusions

Numerous studies in the disciplines of epidemiology, physiology, psychology and biochemistry have all pointed towards a beneficial effect of physical activity on health but the optimal intensity, frequency and duration of physical activity has yet to be established and the mechanisms leading to these health benefits remain uncertain

(98). Older people have altered cardiovascular responses to exercise and reduced peak exercise capacity compared to young healthy people, however the ability to improve exercise capacity through exercise training is maintained into the eighth decade. Improvements in exercise capacity may be due entirely to enhanced peripheral utilisation of oxygen but significant changes in stroke volume and ejection fraction have also been documented through an enhanced use of the Frank Starling mechanism. Diastolic function contributes significantly to exercise capacity and evidence from animal studies suggest that metabolic change altering myocardial relaxation may be a central factor in how exercise training improves exercise capacity. However, further studies looking at the effect of exercise training on diastolic function in humans are needed.

Maximal exercise capacity declines with advancing age



Chapter 2

Age-Related Changes in Myocardial Relaxation using Three-Dimensional Tagged MRI

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Age-Related Changes in Myocardial Relaxation using Three-Dimensional Tagged MRI

2.1 Introduction

Advancing age is associated with marked alterations in left ventricular diastolic function whilst left ventricular systolic function at rest is preserved (12, 28). Studies using echocardiography report a substantial reduction in the peak rate of early diastolic filling between the ages of 30 and 70 years (29) as well as a prolongation of isovolumetric relaxation time (12, 40). The mechanisms underlying these age-related changes are not fully understood but may include decreased calcium uptake by the sarcoplasmic reticulum, which results in prolonged myocardial relaxation (15). Indirect, non-invasive measurement of transmitral and aortic blood flow (22, 29) and invasive assessment of left ventricular pressure decay during isovolumetric relaxation (40) yield conflicting results regarding the changes in myocardial relaxation with aging (12, 40). In addition, these techniques are unable to assess the complex, three-dimensional untwisting motion that occurs during myocardial relaxation and diastole (99). Evaluation of this motion is now possible using magnetic resonance imaging, (MRI) with tagging. This technique uses localised saturation of magnetisation to label specific regions within the myocardium, creating a grid pattern that is fixed with respect to myocardial tissue and becomes deformed as the myocardium moves. Analysis of this deformation then allows direct, non-invasive measurement of myocardial motion with high accuracy. Unique information is thereby obtained regarding rotational, circumferential and longitudinal movement through most of the cardiac cycle and this may provide further insight into age-related changes in diastolic function.

Apical rotation is anticlockwise during systole, (viewed from just below the apex, looking towards the base) and clockwise rotation occurs when the myocardium untwists during relaxation and diastole. Previous studies using MRI have described an untwisting motion that occurs primarily during isovolumetric relaxation and have shown it to be a sensitive parameter for the description of myocardial relaxation (100). This movement has a volume independent component (101, 102) and is prolonged in subjects with left ventricular hypertrophy secondary to aortic stenosis (99, 103). Age-related changes in myocardial relaxation have not previously been assessed using three-dimensional tagged MRI. The aim of this study was to identify changes in myocardial motion during relaxation and diastole that may account for the marked changes in diastolic function documented in older people using Doppler echocardiography. Older, normal subjects were scanned using tagged MRI, the images analysed and the results compared with those from a group of young, normal individuals.

2.2 Methods

2.2.1 Subjects

Subjects were recruited into the study after responding to advertisements within the University of Auckland. The Auckland Human Subjects Ethics Committee approved the study and all participants gave written, informed consent. After evaluating each subject clinically, a 12 lead ECG and transthoracic echocardiogram was performed to exclude important pre-existing cardiac disease or other significant coexisting illness. Exclusion criteria included a history of hypertension, diabetes, ischaemic or valvular heart disease, regular medication for cardiovascular illness, a sitting blood pressure above 160/90 or any significant cardiovascular abnormality on physical examination. On the 12 lead ECG, atrial fibrillation, bundle branch block, pathological Q waves,

left ventricular hypertrophy or changes consistent with myocardial ischaemia resulted in exclusion, as did any significant valvular abnormality, impaired systolic left ventricular function or left ventricular hypertrophy on the transthoracic echocardiogram.

2.2.2 *Echocardiography*

All patients were examined in the left lateral position using an ATL HDI 5000 echo machine. Images were recorded onto videotape and one person blinded to the group of the subject measured the studies off-line. Measurements were recorded at the end of the expiratory phase of the normal respiratory cycle where indicated and an average value from three recorded measurements was obtained for each echocardiographic parameter. Pulsed Doppler transmitral inflow velocities were obtained by placing a 5mm sample volume between the tips of the mitral valve leaflets, with the Doppler beam aligned parallel to the direction of blood flow. The peak early diastolic flow velocity, E the peak transmitral flow velocity in late diastole, A and the ratio of early to late diastolic flow velocities, E/A were all recorded.

2.2.3 *MRI scanning*

In order to reduce the influence of external factors on heart rate and blood pressure, subjects were requested to refrain from drinking caffeine containing drinks and alcohol for 12 hours prior to the scan. Blood pressure and heart rate were noted prior to and following every MRI scan, which was performed more than 16 hours after any period of strenuous exercise. Patients were scanned using a Siemens 1.5 Tesla Vision MRI scanner with a phased array surface coil. Subjects were scanned in the supine position with approximately 15 seconds breath-hold, (at a comfortable position

midway between inspiration and expiration according to a standard protocol) to eliminate respiratory motion artefacts. Three scout scans were performed in order to define the long and short axes of the left ventricle. Eight or nine short axis and six long axis imaging planes were then acquired with 15 to 19 time frames per slice. Standard turbo FLASH cine MRI images were obtained without tagging, (slice thickness 7mm, in-plane resolution ~1mm/pixel and temporal resolution of 40 or 50 ms depending on heart rate). Tagged images were then acquired at the same locations as the untagged images using the same parameters, except for a temporal resolution of 35 or 45 ms, (depending on heart rate). All images were prospectively gated; thus, images could not be acquired during the last 10-15% of the cycle to allow for detection of the R wave trigger.

Tagging

Tags are non-invasive myocardial markers that appear as areas with distinctly different signal intensity to the surrounding tissue. Tagging was achieved using non-selective radio frequency pulses to saturate thin planes of myocardial tissue. Protons in tagged regions are in a different state of magnetization to those in non-tagged regions, emit little signal and appear on the images as black lines in the myocardium. Tagged stripes persist through systole and diastole but fade with time due to longitudinal relaxation, (T1) (104).

A specific tagging sequence, spatial modulation of magnetisation “SPAMM”, using segmented k-space cine imaging with grid tagging on the R wave, was used to create an 8mm tag grid superimposed on the MRI image (105). This grid moves and becomes deformed during cardiac contraction and relaxation. Motion of the grid

reflects motion of the myocardial tissue. A representative set of images is shown in Figure 1, Chapter 2.

2.2.4 *Analysis of tagged images*

Images were stored digitally and analysed “off-line” using dedicated computer software. Tag stripes within the myocardium were located and tracked using a semi-automated tracking procedure based on an active contour model. Each stripe was subdivided into closely spaced points, (two between each stripe intersection) with sub pixel resolution in stripe localisation. Previous experiments on a silicone model have shown that this method produces accurate, unbiased estimates of displacement and shortening or strain (106). The tagged stripes were tracked through the 15-19 images in each slice to determine the exact position of several hundred points in the myocardium through most of the cardiac cycle. Analysis of this data was performed to identify rotation, torsion and average strain or percentage shortening of the myocardium. Through plane motion and out of plane shears were accounted for by analysing the data three-dimensionally.

Left ventricular mass and volumes

Interactive three-dimensional contouring using guide point modelling (106) was performed to define the epicardial and endocardial contours of the left ventricle on the untagged images and thereby calculate volumes and mass by numerical integration. End diastole was defined as the first image in the ECG triggered sequence and end systole was the image with the smallest left ventricular cavity area. The difference between epicardial and endocardial volumes was multiplied by the specific gravity of myocardium (1.05g/ml) and averaged over the cardiac cycle in order to obtain left ventricular mass. The above method does not use geometrical

assumptions and in addition, the epicardium can be defined precisely. This enables left ventricular mass to be calculated more accurately than by other methods such as echocardiography (107).

Apical rotation

The apex was defined as the third of the ventricle furthest from the mitral annulus. Positive apical rotation was defined as the number of degrees of anticlockwise rotation of the apex about the centroid of the left ventricular cavity (99, 103).

2.2.5 Strain analysis

In the analysis of left ventricular shortening or strain, end-diastole was taken to be the first image after the R wave and end systole, (ES) was taken to be the frame of least model volume in the tagged image series. Prolonged relaxation was identified by comparing the amount of strain persisting at a particular time after end systole, (e.g. 150% of ES) or the time taken to relax to 50% of peak value in one group relative to the other. The maximum speed of relaxation was determined by the peak strain-rate after end systole.

Torsion

Torsion is a measure of the degree of twist in the myocardium about the left ventricular long axis. During myocardial contraction, the base of the heart rotates in an opposite direction to the apex. We defined cardiac torsion as the change in angle between two line segments initially oriented in the longitudinal, (L) and circumferential, (C) directions. Both the distance between the apex and base as well as relative rotation of the apex affect this measurement and both may vary between individuals and during the cardiac cycle (99). Torsion angle, (α) was calculated from

the Lagranian strain tensor E in the following standard mathematical equation for calculating strain (108):-

$$\sin \alpha_{CL} = \frac{2E_{CL}}{\sqrt{1+2E_{CC}}\sqrt{1+2E_{LL}}} \quad (1)$$

Circumferential shortening

Average left ventricular circumferential shortening, or strain, describes the size of the left ventricular circumference relative to its initial length. Percentage circumferential shortening was calculated from the Lagranian strain tensor E (108) as

$$\%S_C = (\sqrt{(1+2E_{CC})}-1) \times 100\% \quad (2)$$

This was determined at multiple points in the cardiac cycle by fitting a three-dimensional finite element model to the data and was expressed as a percentage of maximum shortening. Shortening was generally maximal at end systole, and this corresponds to 100% on the time axis, (Figure 3, Chapter 2).

Longitudinal shortening

Longitudinal motion was measured parallel to the long axis of the left ventricle.

Average longitudinal shortening describes the length of the left ventricle as a percentage of its initial length and was calculated from the Lagrangian strain tensor E (108) as:-

$$\%S_L = (\sqrt{(1+2E_{LL})}-1) \times 100\% \quad (3)$$

2.2.4 Statistical analysis

Data were analysed using Students t-test to compare the degree of apical rotation, torsion, circumferential and longitudinal shortening through most of the cardiac cycle

between the two groups. All tests were two tailed and a five-percent significance level was maintained throughout.

2.3 Results

Thirty-three subjects were screened, (15 young, 18 old). Two subjects from the older group were excluded, one after an inferior wall motion abnormality was identified on transthoracic echocardiography and another because of coexisting cryptogenic fibrosing alveolitis. Approximately three-quarters of each group were male. The mean age of the young group was 46 years younger than the older group. Systolic and diastolic blood pressures were significantly higher in the older compared to the young group, (Table 1, Chapter 2). For all subjects included in the study, tagged stripes could be analysed throughout the imaged cycle.

2.3.1 Left ventricular mass and volumes

There were no significant differences in either left ventricular mass or ejection fraction between the two groups, (Table 2, Chapter 2). Left ventricular end diastolic volume was significantly smaller in the older compared to the young group and the ratio of left ventricular mass to end diastolic volume was significantly greater in the older compared to the young group.

2.3.2 Apical rotation and torsion

Peak apical rotation was significantly greater in the old group, ($p=0.003$) as was peak torsion angle, ($p<0.001$), (Table 3, Chapter 2). Figure 4, Chapter 2 shows apical rotation as a function of time indexed to end systole. At 150% of end systole, apical rotation was significantly higher in the older group, (Table 3, Chapter 2). During myocardial relaxation, the time taken for apical rotation to reduce to 50% of its peak

value was significantly longer in the older compared to the young group, ($p=0.007$). The peak velocity of apical rotation during diastole was similar between the two groups, (Table 3, Chapter 2); however, the normalized relaxation velocity i.e. the ratio of peak velocity to peak rotation value was reduced in the older group (-5.1 ± 1.2 vs. $-6.7 \pm 1.2 \text{ s}^{-1}$, $p=0.001$).

2.3.3 *Circumferential shortening*

Peak shortening in the circumferential direction, (%Sc) was not significantly different between the two groups, ($p=0.085$). However, it took significantly longer for circumferential shortening to reduce to 50% of its peak value in the older compared to the young group, ($p=0.001$), (Figure 3, Chapter 2). The peak rate of change of circumferential shortening i.e. lengthening velocity, was significantly slower in the older group, ($p < 0.001$) so that at 150% of end systole significantly more %Sc persisted in the older compared to the young group, ($p < 0.05$), (Table 3, Chapter 2).

2.3.4 *Longitudinal shortening*

Peak longitudinal shortening, (%S_L) tended to be reduced, but did not significantly differ in the older compared to the young group, ($p=0.053$), (Table 3, Chapter 2). The peak lengthening strain rate was reduced, ($p < 0.001$) and time to 50% of peak value was increased, ($p < 0.01$) in the older group. Accordingly, significantly more longitudinal shortening persisted at 150% of end systole in the older compared to the young group, (Figure 2, Chapter 2).

2.4 Discussion

During myocardial relaxation and diastole, the left ventricular myocardium performs a complex movement involving rotational, circumferential and longitudinal motion. Full assessment therefore requires visualisation and analysis of all these movement components. Although measurement of diastolic performance is increasingly recognised as an important part in the assessment of cardiac function, standard imaging techniques are hindered by an inability to image the heart in three dimensions or to directly assess myocardial motion. Measures of diastolic function often rely on assessing blood flow into the ventricles rather than measuring the properties of the myocardium itself. MRI however, is able to examine the motion of the myocardium directly and in three dimensions throughout systole and most of diastole.

2.4.1 Left ventricular mass and volume

An increase in left ventricular mass is often reported to be associated with advancing age but was not seen in this study. Autopsy studies have suggested that coexisting disease rather than advancing age per se causes increased mass in older people and is not seen in normal older individuals (7). Although the numbers included in this study are small, MRI is an accurate method to measure left ventricular mass and volume (109). The increase in mass to volume ratio in the older group has been noted previously (5), correlated with blood pressure, ($R^2 = 0.37$, $p < 0.001$) and may be due to increased afterload.

2.4.2 Systole

In individuals carefully screened to exclude coexisting disease, resting left ventricular systolic function is thought to be unaffected by aging (8, 12, 22, 40). No

significant differences in global systolic chamber function, assessed by left ventricular ejection fraction, were observed between the two groups in this study. Although peak apical rotation and torsion were increased, peak longitudinal and circumferential shortening were not significantly different. Similar findings using MRI with tagging have been described in people with left ventricular hypertrophy secondary to aortic stenosis (99, 103) and in patients with hypertrophic cardiomyopathy (110). No correlation between apical rotation or torsion and mass to volume ratio was found, but both peak %S_C and peak %S_L decreased with increased mass to volume ratio, ($R^2 = 0.39$, $p < 0.001$ and $R^2 = 0.53$, $p < 0.001$ respectively). Whilst changes in mass to volume ratio may account for differences seen at end systole, they do not explain the differences observed during myocardial relaxation and diastole.

2.4.3 *Myocardial relaxation and diastole*

More circumferential and longitudinal shortening persisted into diastole, together with increased apical rotation and ventricular torsion in the older group. Thus, in this group, the ventricle is partially rotated and contracted, whilst younger individuals have an almost fully untwisted and relaxed ventricle during the same time period. In a study of patients with aortic stenosis, MRI tagging identified delayed reversal of apical rotation and a decreased, normalized rotation velocity during diastole (99, 103). Our results indicate that increasing torsion together with reduced relaxation strain rates also occur to some degree due to aging in healthy volunteers, highlighting the need for age-matched controls in studies of diastolic function. In this study, peak %S_C and %S_L lengthening velocities decreased with increasing mass to volume ratio, ($R^2 = 0.56$, $p < 0.001$ and $R^2 = 0.43$, $p < 0.001$ respectively); however, analysis of covariance showed that these strain rates were still significantly lower in the older

group after correcting for differences in mass to volume ratio, ($p < 0.001$ in each case). It is possible that the differences in strain rates were due to the different blood pressures seen between the groups. However, mass to volume ratio, which correlated significantly with blood pressure, was not accountable for all of the differences in diastolic strain between the groups. Thus, blood pressure may not be the cause of the changes seen in diastole in the older group.

Doppler echocardiography identified significant differences in both early, (E) and late, (A) transmitral flow velocities between the two groups, (Table 1, Chapter 2). Previous reports have also identified reduced blood flow during early diastole in older compared to young individuals (22, 29, 31, 111). This reduction in early diastolic filling is thought to be due, in part, to an intrinsic aging process that affects left ventricular compliance (22). Blood will flow less freely into a partially contracted and rotated ventricle than into one that is fully relaxed. By including longitudinal and circumferential movement, together with apical rotation and torsion into the study, observations using MRI have been extended to a full, three-dimensional description of myocardial motion. Thus, MRI with tagging is able to observe changes in three-dimensional myocardial motion that describe a mechanism which could explain the delayed, reduced early left ventricular filling previously identified using echocardiography.

Prolonged myocardial relaxation has been described in senescent rats and is thought to be due to reduced uptake of calcium into the sarcoplasmic reticulum (15). This study supports observations made in animals, that the aging process is associated with a prolongation of myocardial relaxation. Previous studies have described a prolongation of apical untwisting during relaxation and diastole in patients with

severe left ventricular hypertrophy (103) or hibernating myocardium (112) but a prolongation of material relaxation associated with increasing age has not previously been described.

Changes in myocardial relaxation and diastole are sensitive markers of myocardial disease or dysfunction (113) and previous studies have suggested that torsion may be less volume and load dependent than current techniques as a measure of diastolic function (102, 114). In addition, the velocity of the mitral annulus in the longitudinal direction can be used as a surrogate for longitudinal strain relaxation rate and is a relatively preload independent index of relaxation (34).

2.4.4 *Limitations of the study*

Changes in myocardial relaxation cannot be assumed to be associated with reduced early diastolic flow because simultaneous measurement of left ventricular filling and myocardial movement was not performed. However, echocardiographic assessment did confirm a reduction in the peak early diastolic filling velocity in the older compared to the young group, (Table 1, Chapter 2). Newer echocardiographic measurements of diastolic function such as annular velocities measured using tissue Doppler imaging, E' were not available for inclusion into this analysis.

In the present study, information regarding end diastole was not available.

Alterations in the tagging sequence may improve tag stripe resolution and persistence in future studies and allow acquisition of the atrial component of left ventricular filling.

Conclusive evidence of the absence of important coronary occlusive disease was not obtained by performing coronary angiography on the older study participants. Thus, coexisting occult cardiac disease may have accounted for some of the differences seen between the groups.

Although the labour intensive off-line analysis continues to be a limiting factor for routine clinical evaluation of tagged MRI images, this technique may play an important role in the assessment of myocardial relaxation and diastolic function in the future.

2.4.5 *Conclusions*

- MRI with tagging can be used to quantify three dimensional myocardial motion through most of the cardiac cycle.
- Myocardial relaxation is significantly delayed and reduced in older normal individuals as evidenced by a persistence of apical rotation, circumferential and longitudinal shortening and slower rates of lengthening and reversal of apical rotation.

Table 1 Chapter 2**Baseline characteristics**

	Young	Old	p
	Mean (SD)	Mean (SD)	
Age (years)	22.3 (2.6)	68.8(4.4)	p < 0.0001
	Range (19-26)	Range (60-74)	
Male/Female	11/4	10/6	p = 0.53
Weight (kg)	74.4 (15)	74.8 (17.9)	p = 0.54
Height (cm)	184.7 (11)	169.5 (8.7)	p = 0.15
Heart Rate	69.7 (9.8)	70.3 (11.3)	p = 0.89
BSA (kg/m ²)	1.83 (0.25)	1.84 (0.25)	p = 0.99
Systolic BP (mmHg)	123.5 (14.5)	146 (15.6)	p < 0.0001
Diastolic BP (mmHg)	65.5 (5.54)	83.2 (9.92)	p < 0.0001
E velocity (m/s)	74.2 (15.9)	46.2 (10)	p < 0.0001
A velocity (m/s)	41.3 (7.8)	57.9 (12.5)	p < 0.0001

Table 2 Chapter 2**Left ventricular mass and volume measurements**

	Young	Old	p
	(n=15)	(n=16)	
	Mean (SD)	Mean (SD)	
Mass (g)	143.0 (34)	146.0 (39)	0.82
Ejection fraction (%)	70.7 (3.0)	69.3 (6.6)	0.46
Stroke volume (ml)	97.1 (18.8)	79.8 (19.5)	0.018*
End systolic volume (ml)	40 (9.2)	36 (12.7)	0.259
End diastolic volume (ml)	137 (26.7)	115 (27.1)	0.031*
Mass: EDV ratio	1.04 (0.1)	1.28 (0.3)	0.006*

*** = p<0.05**

Table 3 Chapter 2

Material motion and relaxation parameters

Mean (SD)

		Peak value	150%ES	PRR	T50% (ms)
Old	Apex rotation	13.9 (2.2) ^{o †}	5.8 (2.2) ^{o *}	71.0 (21.1) ^{o /s}	149 (50) [†]
	Torsion	6.5 (1.0) ^{o ‡}	2.8 (0.9) ^{o *}	36.4 (8.1) ^{o /s}	174 (99)
	%S_C	18.7 (3.1)%	12.0 (2.9)% [*]	76.2(28.5)%/s [‡]	234 (49) [‡]
	%S_L	15.5 (2.5)%	10.5 (2.0)% [*]	62.7(21.3)% /s [‡]	228 (61) [†]
Young	Apex rotation	10.9 (3) ^o	3.0 (1.9) ^o	71.0 (19.2) ^{o /s}	109 (19)
	Torsion	5.1 (1.1) ^o	1.8 (0.9) ^o	31.8 (10.1) ^{o /s}	130 (41)
	%S_C	20.2 (1.1)%	8.2 (3.1)%	142.5(16.6)% /s	155 (16)
	%S_L	16.9 (1.3)%	7.9 (3.2)%	122.5(19.6)% /s	174 (24)

%S_C: %Circumferential Shortening, **%S_L**: %Longitudinal Shortening,

150%ES: value at 150% of end systole, **PRR**: peak rate of relaxation,

T50%: time from peak to 50% of peak

***p<0.05, † p<0.01, ‡ p<0.001**

Figure 1 Chapter 2

Myocardial tagging

*Short axis cardiac images from an older individual showing end diastole and
end systole*

End-Diastole

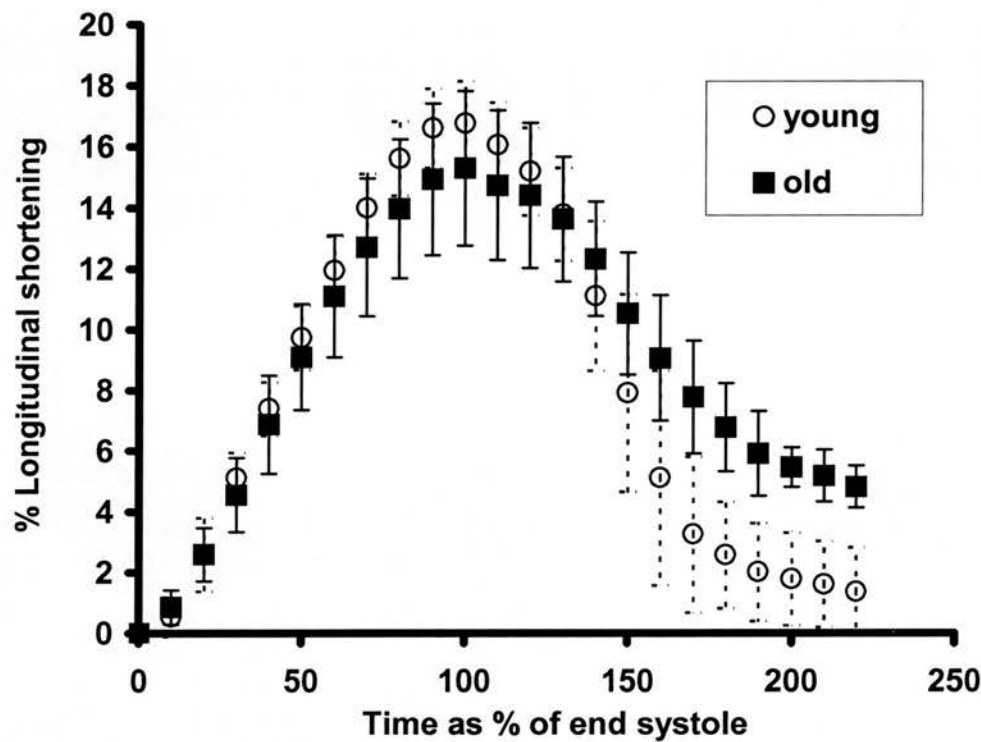


End-Systole



Figure 2 Chapter 2

Longitudinal shortening in young and older normal volunteers



*Values for shortening expressed relative to time to end systole
in order to overcome differences in heart rates*

Figure 3 Chapter 2

Circumferential shortening
as a function of time to end systole

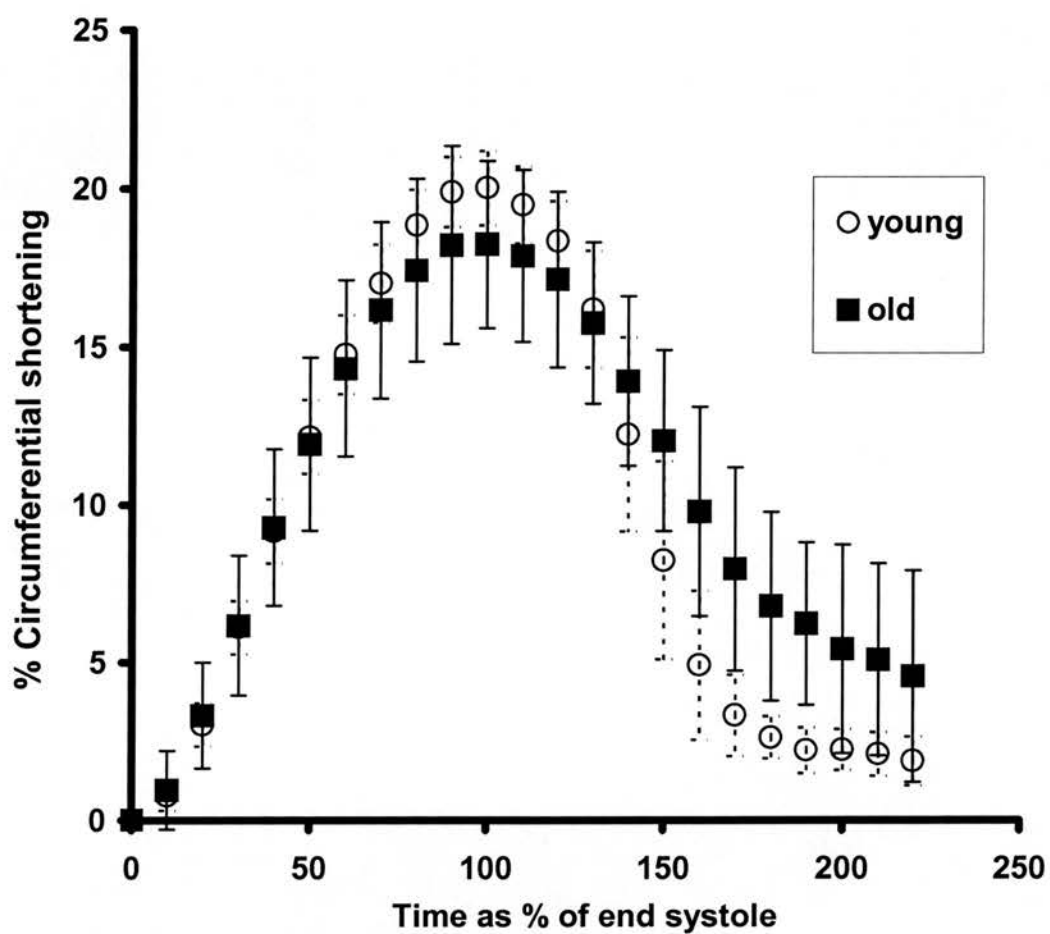
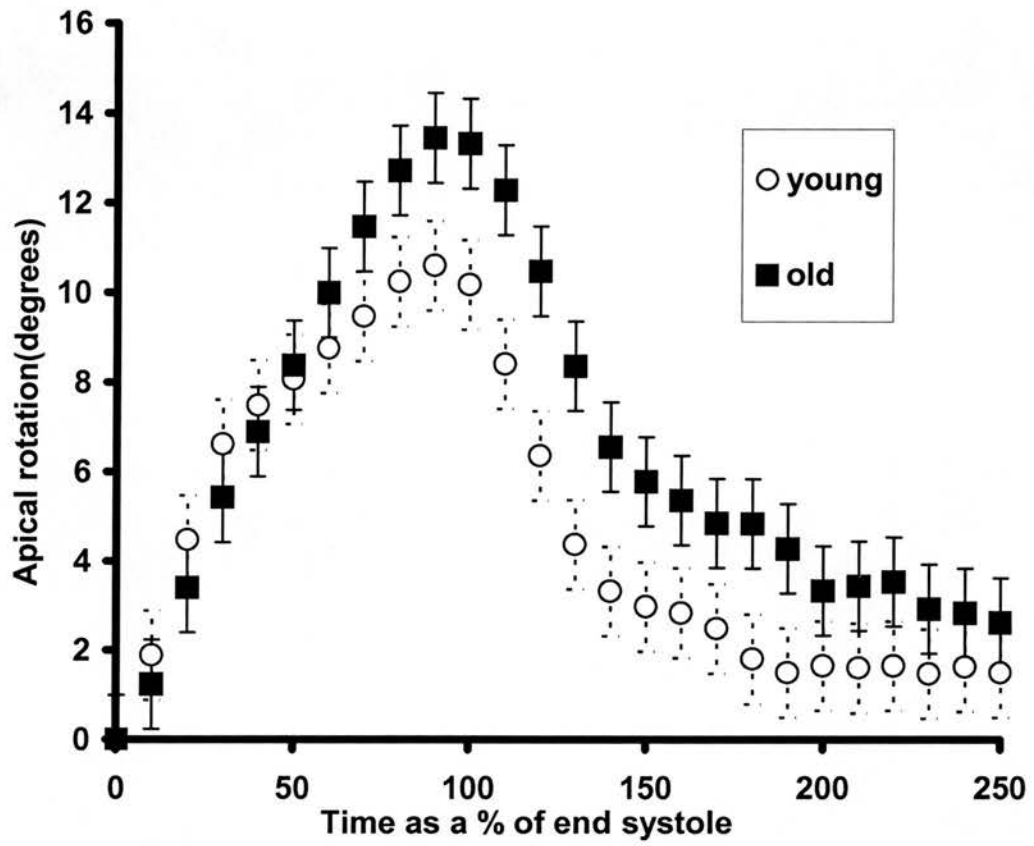


Figure 4 Chapter 2

Apical rotation as a function of time to end systole



Chapter 3

Modification of Age-Related Changes in Cardiovascular Function Following Exercise Training Methods

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Modification of Age-Related Changes in Cardiovascular Function Following Exercise Training: Methods

3.1 Study rationale

3.1.1 *Age-related changes in cardiovascular function*

Aging may be defined as a reduction in the capacity of a bodily system. Some of the age-related changes in cardiovascular function are physiological or due to coexisting diseases and some are as a result of inactivity and are less marked in trained elderly subjects (28). Measurement of maximum oxygen uptake, (VO_2max) is a common method of evaluating the capacity of the cardiovascular system. Exercise capacity, measured using VO_2max , reduces progressively with age by about 10% per decade (28). There may be multiple causes for this, including a lowering of peak heart rate, changes in stroke volume with exercise (53, 54) and a decline in muscle mass and strength (53).

3.1.2 *Diastolic function*

One of the most striking changes in cardiovascular function with advancing age is an alteration in left ventricular diastolic function (73). For the purposes of this study, diastolic function is defined as left ventricular filling and includes isovolumetric myocardial relaxation, (which is considered by some to be a part of systole rather than diastole). Animal studies show myocardial relaxation to be an energy dependent process and provide mechanisms at a molecular level with which age-related diastolic changes can be explained (15, 48). The rate of myocardial relaxation and diastolic filling depends upon the ability of the sarcoplasmic reticulum to sequester calcium. A reduced rate of calcium transport by the cardiac sarcoplasmic reticulum

leads to prolongation of cardiac muscle relaxation and impaired left ventricular filling (15). This process has been shown to be slower in senescent rats and concentrations of a sarcoplasmic reticulum protein responsible for calcium transport have been shown to be lower in aging human myocardium (16). In addition, a change in myosin isoform type with advancing age, from fast to slow types, has been identified in animals and this also slows the rate of calcium re-uptake (12) and thus myocardial relaxation.

Assessment of diastolic function

Echocardiography allows measurement of Doppler transmitral flow velocities for assessment of early and late diastolic left ventricular filling (39). In the elderly, early left ventricular filling is delayed and reduced, whilst late ventricular filling is augmented, resulting in a lower ratio of early, (E) to late, (A) filling, (E/A ratio) (22, 29). Despite being unaffected by physiological hypertrophy (81), transmitral flow velocities are heart rate and load dependent (24, 115). Thus, changes in diastolic function following exercise training or between master athletes and sedentary controls using transmitral flow velocities could be due to different heart rates. Changes in diastolic function after exercise training therefore need to be assessed in ways that are less heart rate dependent, such as with tissue Doppler imaging.

3.1.3 *Diastolic function and exercise capacity*

Diastolic filling, measured using Doppler transmitral flow velocities, has been shown to correlate significantly with exercise capacity in normal people of varying ages (51). VO_2max correlates with resting early mitral flow, ($r=0.8$) and even more closely with E/A ratio, ($r=0.87$) in healthy people (51). In patients with heart failure, diastolic filling parameters correlate strongly with symptoms of breathlessness, peak

exercise capacity, (VO_2max) and prognosis (96) and exercise training improves both VO_2max and diastolic filling despite no change in ejection fraction (116). Patients with diastolic heart failure have a markedly reduced ability to augment stroke volume or cardiac output with exercise and this leads to pronounced symptoms of breathlessness and a reduction in VO_2max (22). Therefore, it is possible that changes in diastolic function are responsible for changes in exercise capacity in healthy older people.

3.1.4 *Previous studies using exercise training*

Trained elderly subjects exhibit attenuated age-related alterations in cardiac function and exercise capacity suggesting that some changes are, at least in part, reversible (76, 81, 82). The ability of the cardiovascular system to respond to endurance training appears to be maintained into the 70's, with studies showing improvements in VO_2max of between 10 and 20% in elderly people (46). Studies examining the effect of exercise training in older individuals have previously concentrated on indices of left ventricular systolic function (47) and maximal oxygen consumption (89). Convincing evidence that the improvement in VO_2max with exercise training is due to central rather than peripheral adaptation is lacking (90). Small changes in left ventricular end diastolic diameter with augmented stroke volume and peak cardiac output during exercise have been observed in some exercise training studies in the elderly (63, 76). Most studies of exercise training in older people have, however, been observational or non-randomised and few have included women as participants despite this being the predominant gender in older age.

3.1.5 *Exercise training and diastolic function*

The expected pattern of diastolic filling normally seen in the elderly is modified in the older athlete (83) suggesting that exercise training may alter diastolic abnormalities. Exercise training in senescent rats has been shown to improve re-uptake of calcium into the sarcoplasmic reticulum and improve myocardial relaxation (15). Studies that have examined the effects of a period of exercise training on diastolic function in humans are small in number and have reported variable results (70, 80, 90). Most have used transmitral Doppler flow velocities or radionuclide techniques to measure left ventricular filling. An increase in early and decrease in late left ventricular filling velocities after exercise training has been observed (63, 80). These findings would suggest that exercise training may alter diastolic filling but the dependence of the methods used on heart rate as well as the absence of control groups in these studies make this conclusion questionable.

3.1.6 *New echo measures of diastolic function*

Tissue Doppler imaging is a simple non-invasive echocardiographic marker of myocardial relaxation and diastolic function (117, 118) that overcomes the haemodynamic dependence of transmitral flow velocities. This technique applies the Doppler principle to record low amplitude velocities generated by the motion of the left ventricular wall or the mitral annulus during left ventricular filling and gives a measurement of the rate of longitudinal dimension or volume change during diastole (32). Pulsed wave tissue Doppler imaging of the mitral annulus in normal, healthy individuals shows three major distinctive waves, a positive wave towards the apex during systole and two waves away from the transducer during diastole. The two diastolic waves appear as a mirror image of the Doppler transmitral flow velocity

tracing and correspond to mitral annular velocity during early left ventricular filling, E' and to mitral annular velocity during atrial contraction, A' , (Figure 1, Chapter 3). Unlike Doppler transmitral flow velocities, these measurements show a steady decline in amplitude from normal to advanced diastolic impairment, are relatively load independent and are easy to obtain even when standard echo images are not possible (32). They correlate closely with both systolic and diastolic values of cardiac long axis function obtained using M-mode (33) and show a significant fall in the ratio of myocardial E' to A' with increasing age (33, 34, 35). Although reversal of the transmitral E/A ratio occurs in the seventh decade, reversal of the E'/A' ratio occurs earlier, in the fifth decade (32). Myocardial velocities measured from the posterior wall of the left ventricle also show a gradual fall in both systolic and diastolic values with increasing age (119, 120).

E' reflects global left ventricular diastolic function and correlates, in normal subjects, with conventional measures derived from transmitral flow velocities as well as with the time constant of left ventricular relaxation, τ , (121) and left ventricular end diastolic pressure (32). However, E' should not be viewed as a direct measure of myocardial relaxation because the correlation with invasive measures of myocardial relaxation is modest at best (38, 122). By combining the influences of transmitral driving pressure, E , (i.e. blood flow) and myocardial relaxation, E' , (myocardial velocity) during early diastole, the most sensitive and specific marker to estimate left ventricular end diastolic pressure non-invasively using echocardiography is obtained, E/E' (122). Data regarding this measurement and age are not yet available but promise to provide additional important information regarding the changes in diastolic function associated with increasing age.

Studies comparing athletes with sedentary individuals, using tissue Doppler imaging, have shown a partial reduction in the expected age-associated changes in diastolic function (85) but these techniques have not previously been used to assess changes in diastolic function as a result of exercise training.

3.1.7 *Changes in cardiac structure using magnetic resonance imaging (MRI)*

MRI is a sensitive method by which changes in left ventricular mass occurring as a result of exercise training can be measured (116). However, little data exist regarding changes in cardiac structure or function using MRI following exercise training. Thus, this study has the potential to provide important mechanistic information about the effects of exercise training on cardiac structure and function assessed by MRI.

3.1.8 *Conclusions*

In summary, elderly people without evidence of cardiac disease commonly have significant age-related changes in diastolic function. Exercise training is effective and feasible in this age group and results in increases in VO_2max of 10 to 20% (87). Changes in diastolic function as a result of exercise training in normal elderly people can now reliably be measured using imaging modalities that are independent of heart rate and load conditions. As exercise capacity correlates strongly with diastolic function, exercise training is an appropriate intervention with which to assess the permanence and significance of age-related diastolic changes in the elderly. This study will provide new information regarding cardiovascular responses to exercise training in the elderly and in particular the mutability of age-related diastolic changes.

3.2 Study hypothesis

The hypothesis on which this study was based is that age-related changes in cardiac diastolic function in normal subjects could be altered following a period of exercise training.

3.3 Study design

The study was a randomised, controlled trial, comparing the effects on cardiac diastolic function, of a six-month period of exercise training in one group with a sedentary control group. Because of the lack of current available evidence regarding exercise training and older people from randomised controlled trials, it was felt that this type of trial would contribute appreciably to current evidence regarding exercise training and cardiac function.

3.3.1 Trial participants

Because of the lack of evidence regarding exercise training in older women, both male and female participants were included in the trial, despite suggestions that there are substantial gender differences in responses to exercise training (62).

Diastolic abnormalities are present in 85% of people over the age of 70 years of age (27) and early transmitral flow velocity falls by 50% between the ages of 30 and 70 years (29). However, as the incidence of cardiovascular disease rises steeply in people aged over 60 years, we decided to recruit older people from the community with diastolic transmitral flow patterns consistent with old age but did not concentrate solely on people over 70 years of age in order to attain adequate recruitment rates.

3.3.2 *Recruitment*

This study aimed to recruit community dwelling older people who had no significant cardiovascular disease. As this group of people is unlikely to regularly attend medical facilities, advertising in the community was felt to be the most appropriate method by which to recruit volunteers. Previous studies have shown that allowing family members or friends to participate in a study increases both recruitment and participation rates (123). Therefore, married couples, siblings and neighbours of volunteers were also included in the trial if they wished.

Recruitment took place over a 6-month period, between January 2001 and June 2001. During this time 63 people were randomised into the trial. This number slightly exceeded the total number of people expected to be included into the trial (60) in order to allow for subjects who might drop out after randomisation. Additional subjects were unable to be randomised after the end of June because there was insufficient time to provide six months of exercise training between randomisation and closure of the exercise training facility over the Christmas period. Significant variations in physical activity and fitness occur between winter and summer months with a tendency to increased activities in the summer. In order to allow for this potential variation in fitness at baseline, the recruitment period spanned a six month period.

3.3.3 *Advertisements*

Advertisements were placed in local free newspapers that are delivered weekly to households in Auckland. Newspapers that covered areas in the city that were adjacent to the training facility were targeted as it was felt that distances to the training facility from the subjects home should be as small as possible in order to aid compliance and reduce transport costs. These areas comprised a mixture of wealthy

as well as lower socio-economic residential housing. A total of six adverts were placed over the six month period in three separate newspapers. The adverts were aimed at individuals aged over 60 years who were interested in taking part in a program, which assessed cardiovascular function and physical fitness with the possibility of allocation to a six month exercise-training program. A sample advert is attached, (Appendix 1). Adverts were also placed in Age-Concern and Rotary Club newsletters. These newsletters have a larger area of distribution, the former comprising the whole of Auckland city and the latter Central and South Auckland areas only. In addition, 15 posters were placed in libraries, community centres, retirement villages, bowling and bridge clubs in the areas of the city adjacent to the training facility.

3.3.4 Telephone contact

A contact phone number with message recording capabilities was included on both adverts and posters. Possible trial participants who responded to the advert or posters were contacted by phone if they had left a message indicating an interest in the trial. Further details regarding the trial were supplied to the callers who were also asked several simple screening questions over the phone to assess their eligibility for the trial. These questions aimed to identify the presence of current or previous cardiac disease, diabetes or hypertension and whether regular, prescribed medication was being taken. Following this initial contact, an information sheet was sent by post to all interested subjects who were eligible to take part.

A total of 110 people were sent information sheets and of these, 87 agreed to be seen in the hospital department for an initial screening visit. A large number of other callers were excluded due to the presence of coexisting conditions that became

apparent during the screening questionnaire. Reasons stated by other interested persons for their decision not to take part in the trial included inadequate time for the training regimen or lack of transport to the training facility. Potential participants were advised at recruitment that only approximately 50% of screened participants would undergo exercise training but that pre study levels of activity should be maintained for those subjects randomised into the control group. This resulted in some potential participants deciding not to continue in the study, but did not adversely affect overall recruitment.

After receiving an information sheet, participants either contacted the principal investigator themselves, or were contacted by the principal investigator who arranged a screening appointment. Married couples were both given screening appointments. In the event that both successfully completed the screening tests without being excluded, they were treated as a single subject for the purpose of randomisation, as it was assumed that compliance and other subject related factors would be identical for each person. Petrol vouchers were offered to participants in order to aid transport costs to and from the hospital appointments.

3.3.5 *Coding system*

Subjects were allocated a registration number at enrolment, prior to their assessment of eligibility to be randomised, (e.g. subject 45). If any subject failed to arrive for their initial appointment their number was transferred to the next subject that attended the department. All data was subsequently recorded using this study number as well as the subjects' two initials.

3.4 Screening

The Italian Longitudinal Study of Aging and other population-based studies have identified that within an older population, cardiovascular disease is both common and often undiagnosed (124). The major objectives of pre-participation cardiovascular screening were therefore to identify persons with cardiovascular disease as well as those with risk factors for disease development. Screening is important for two main reasons. Firstly, moderate or strenuous physical exertion may trigger ischaemic cardiac events, particularly among persons not accustomed to regular physical activity and exercise (125, 126). Although screening procedures are not perfect for identifying the rare individual who is at risk, the overall risk for the study population as a whole is decreased if proper screening precautions are implemented. Secondly, this study attempted to examine the effect of exercise training on age-related changes in cardiovascular function without the confounding influence of coexisting disease. Subjects to be included in the study were therefore required to have no evidence of coexisting cardiovascular disease.

3.4.1 *Risks associated with exercise training in an elderly population*

Whilst the benefits of regular exercise are not disputed, there is a small risk of death or myocardial infarction when older people undergo physical exercise (52). The prevalence of myocardial infarction in Americans aged 60 to 69 years is 18% and 9.7% for men and women respectively. Younger populations have a significantly lower prevalence of myocardial infarction and thus the risk of developing a cardiac event related to exercise is lower for young compared to older populations. After excluding people with known heart disease, the risk of a primary cardiac event during high intensity exercise in a clinically healthy population has been reported to

be 0.55 events per 100 000 men per year (126). In the TIMI II trial, physical activity preceded myocardial infarction in 18.7% of patients and the incidence of myocardial infarction during cardiac rehabilitation programs has been reported as 1 per 294 000 person hours. Overall, the absolute incidence of death during exercise in the general population is low, approximating to 6 per 100 000 in middle-aged men. However, similar estimates for either women or the elderly are not available (126). Thus, adequate screening and evaluation are important to identify and counsel persons with underlying cardiovascular disease before they begin exercising to moderate or vigorous levels (52).

3.4.2 *Exclusion of coexisting cardiovascular disease*

There is a high prevalence of "silent" coronary artery disease and unrecognised hypertension in the elderly (127). Non-invasive screening tests to identify "silent" coronary heart disease are limited by low pre-test probability in an asymptomatic population, particularly when the resting electrocardiogram, (ECG) and echocardiogram are normal (52). In addition, all tests used for the diagnosis of coronary artery disease have considerable overlap in the range of measurements for the normal population and those with heart disease. The addition of thallium imaging to the exercise test has been shown to substantially increase the predictive value of the exercise data in certain populations, but coronary angiography would have been required in order to be confident that significant coronary artery disease was not present in the study participants. However, in our study, further testing was not thought to be appropriate or necessary in view of the increased cost, time restraints and potential harm that could be associated with these investigations (125). In addition, we were keen to minimize the number of clinic visits during the trial so as to aid compliance.

The following assessment was carried out for all potential subjects. This assessment was performed in order to be as sure as possible that no cardiovascular disease was present without performing invasive and costly investigations.

3.4.3 *Medical history*

All potential participants were asked to provide information regarding their medical history, current medication and risk factors for cardiovascular disease. Exclusion criteria included: -

- A past history of hypertension, diabetes, cardiovascular or valvular heart disease.
- The presence of non-cardiac serious conditions such as cancer or significant respiratory disease.
- Regular medication for cardiovascular illness.
- Medications for non-cardiac conditions such as alpha-blockers as treatment for prostate problems. These medications have significant effects on both blood pressure and heart rate and were therefore included in the exclusion criteria as they may affect diastolic function.
- Symptoms suggestive of an underlying cardiac abnormality such as chest discomfort on exertion.
- People with orthopaedic problems that would prevent them from undergoing exercise training.

3.4.4 *Physical examination*

Blood pressure was recorded from the brachial artery using a mercury sphygmomanometer with the subject in the sitting position. Two readings were

recorded and the average taken. Hypertension was thought to be significant if there was any ECG or echo evidence of left ventricular hypertrophy as well as blood pressure recordings above 160/90 or if the subject had previously been treated for hypertension. This slightly high value for blood pressure was chosen in order to include possible candidates whose blood pressure may have been transiently high due to unfamiliar surroundings. Pulse rate was taken as the heart rate that was recorded on the 12 lead ECG and this was always recorded immediately after the general physical examination. In this way standardised conditions for each subject in the study was created for recording resting heart rate.

3.4.5 ECG

A resting, 12 lead ECG was recorded for all potential participants. Abnormalities on the resting 12 lead ECG such as atrial fibrillation, left bundle branch block, pathological Q waves, criteria for left ventricular hypertrophy or changes consistent with myocardial ischaemia resulted in exclusion.

3.4.6 Exercise tolerance test

It is well known that an individual can have significant coronary artery disease in the absence of symptoms or signs and in the presence of a normal ECG and a normal exercise test. However, exercise testing is a well-established procedure that has been in widespread clinical use for many decades and is the best non-invasive method for detecting significant occult coronary artery disease. Although it is generally safe, the reported risk of death or myocardial infarction is up to a rate of 1 per 2500 exercise tests, although the complication rate and accuracy for asymptomatic and low risk individuals has never been defined (125). The American Heart Association and American College of Cardiology, (AHA/ACC) joint guidelines recommend

evaluation of asymptomatic men older than 40 years and women over 50 years who plan to start vigorous exercise, especially if previously sedentary. Although subjects in the study were elderly, they were asymptomatic with no or only one risk factor for cardiovascular disease and were therefore a low-risk group for the presence of coronary artery disease. The AHA/ACC guidelines on exercise testing recommend that an appropriately experienced physician supervise the tests, (this was the principal investigator) (125). In addition to providing information regarding safety, an exercise test is also useful in formulating each individual's initial exercise training prescription.

Exercise tolerance test protocol

Each participant underwent a treadmill exercise test using the standard Bruce protocol. The ECG, heart rate and blood pressure were monitored during each stage of exercise and the subject was monitored continuously to identify arrhythmia or ST segment change. A positive test, which would exclude the subject from further involvement in the study, was defined as the development of symptoms consistent with angina and at least 1 mm of flat or down-sloping ST depression in one or more leads, or a reduction in blood pressure of greater than 20 mmHg with increasing functional load or the development of left bundle branch block or significant arrhythmia during or shortly after the test. 1mm of horizontal or down sloping ST segment depression has a specificity of approximately 84% for angiographically significant coronary artery disease in symptomatic individuals. The sensitivity varies from 40% for single vessel to 90% for triple vessel coronary artery disease but has little prognostic value for asymptomatic individuals unless an exercise ST segment response of 2mm or more is accompanied by symptoms or other abnormal responses on exercise (52).

3.4.7 *Echocardiogram*

Most of the participants that attended for screening also underwent an echocardiographic examination of the heart. This was performed immediately after the ECG and physical examination had been performed.

Any significant valvular abnormality, which was defined as valvular regurgitation of a greater severity than mild, or any degree of valve stenosis more than trivial, as well as regional wall motion abnormalities, left ventricular systolic impairment or left ventricular hypertrophy resulted in exclusion. Enlargement of the right heart with significant tricuspid regurgitation, evidence of a ventricular septal defect, atrial septal defect, cardiomyopathy or significantly dilated aortic root were also exclusion criteria.

Echo protocol

Patients were examined in the left lateral position using an ATL HDI 5000 echo machine. Images were recorded onto optical disc, (Image Vue, Nova Microsonics) as well on videotape. All standard 2D views were performed as well as pulsed Doppler transmitral flow velocities, pulmonary vein flow velocities and tissue Doppler imaging of the lateral and septal aspects of the mitral annulus. The following measurements were recorded: -

Standard views

Parasternal long axis view: -

- Left atrial diameter by M mode through the aortic root
- Interventricular septal wall thickness
- Posterior left ventricular wall thickness

- Left ventricular cavity dimension at end diastole, (LVEDD) and end systole, (LVESD)

Apical four chamber view: -

- Transmitral flow velocities at the mitral leaflet tips, (Figure 2, Chapter 3)

Pulsed Doppler transmitral flow velocities were recorded by placing a 5mm sample volume between the tips of the mitral valve leaflets with the Doppler beam aligned parallel to the direction of blood flow. The peak velocity during early diastolic filling, E and peak velocity during late diastolic filling, A were recorded as well as the E wave deceleration time and E/A ratio. The subject was also asked to perform the Valsalva manoeuvre. A recording of transmitral flow was performed throughout and measurements of E, A and E deceleration time were recorded during the final seconds of the manoeuvre. The Valsalva manoeuvre causes intracardiac pressures to change and allows differentiation of pseudonormal from normal transmitral flow patterns. A transmitral flow pattern is thought to be pseudonormal if, after the Valsalva manoeuvre, the E/A ratio decreases by more than 25%, or is less than 1.0. In this way, diastolic function can be assessed, by assigning a number to each grade of left ventricular filling pattern (128). Impaired myocardial relaxation is assigned grade 1, an intermediate filling pattern is assigned grade 2, (pseudonormal filling) and restrictive filling is assigned grade 3 (129).

- Isovolumetric relaxation time

Isovolumetric relaxation times were recorded by placing a 5-mm sample volume in the left ventricular outflow tract. This was positioned to give a clear signal incorporating both the aortic valve closing signal and the onset of transmitral flow. IVRT is the time interval between aortic valve closure and the onset of mitral inflow.

- Pulmonary vein flow velocities

These were obtained by placing a 5-mm sample volume at least 1 cm into the right or left upper pulmonary vein. The following measurements were made from the recordings obtained: -

- Peak velocity during systole, S
- Peak velocity during diastole, D
- A wave size and duration
- Left ventricular systolic function

In the apical two and four chamber views, the endocardial-blood border was identified and traced. This was performed at end diastole, defined as the time corresponding to the R wave on the ECG. A second measurement was made at end systole, which was defined as the smallest cavity volume in the cardiac cycle. Thus, ventricular areas in two orthogonal planes were obtained both at end diastole and at end systole.

Calculations of left ventricular volumes were then made using the modified biplane Simpson's rule. The difference between end diastolic and end systolic volumes is calculated to be the ejection fraction.

- Left atrial area

This was measured by tracing the left atrial border with the image frozen in systole and again in diastole. Measurements were taken in apical two chamber and apical four chamber views so that an estimate of left atrial volume could be made.

Tissue Doppler imaging

Tissue Doppler imaging of the mitral annulus from the four chamber apical view was chosen in order to obtain a quantitative assessment of left ventricular myocardial longitudinal velocity, (Figure 1, Chapter 3). This view minimizes the incidence angle between the Doppler beam and longitudinal wall motion. Tissue Doppler imaging was used to record mitral annular velocities from both the septal and lateral aspects

of the mitral annulus. The cursor was positioned carefully to ensure that mitral annular movement was in a plane parallel to the cursor. Gain and scale were altered in order to maximize the size of the Doppler signal and reduce measurement inaccuracies. The following measurements were made: -

- Peak annular motion during early diastole, E'
- Peak annular motion during late diastole, A'
- Peak annular motion during systole, S
- E/E' ratio

Echo analysis

One person blinded to the group of the subject measured the studies off-line.

Analysis used the leading edge-to-leading edge method for all measurements in accordance with the American Society of Echocardiography guidelines.

Measurements were recorded at the end of the expiratory phase of the normal respiratory cycle where indicated. For each parameter, three measurements were taken and an average value recorded.

3.5 Blood tests

20 ml of venous blood were taken by venesection from a vein in the antecubital fossa after the subject had been resting for 15 minutes. 10 ml of the blood sample were collected into a tube that had been stored on ice and was subsequently kept at zero degrees until it was centrifuged. Two other plain, non-heparinised tubes, each containing 5ml of blood were collected. A fourth tube containing lithium heparin was used to collect a 5 ml sample of blood that was sent immediately to the laboratory within the same hospital. This blood was subsequently analysed to give values for non-fasting lipids, random glucose and serum creatinine.

3.5.1 *Serum glucose*

A random glucose level served to identify undiagnosed diabetes. Random values at the upper range of normal or above were noted and the subjects then asked to attend a local laboratory where a fasting glucose sample as well as glycosylated haemoglobin level was measured. If the fasting glucose level was above 7 mmol/l and glycosylated haemoglobin values were greater than 5.6 mmol/l, then diabetes was considered likely to be present. Oral glucose tolerance tests were not performed. Altogether, five subjects were required to provide fasting samples for glucose estimation. These were all within the normal range apart from one woman who was subsequently excluded from the trial because of the diagnosis of diabetes.

3.5.2 *Lipid profile*

The effects of exercise training on lipid concentrations in an older population are unclear (130). Cholesterol, low density lipoprotein, (LDL) levels and high density lipoprotein, (HDL) concentrations have previously been shown to change with exercise training in young and middle aged adults, but most documented evidence regarding the changes in lipid profile with exercise in older people comes from observational or non-randomised trials (91). It is however, generally accepted that HDL cholesterol levels increase whilst LDL cholesterol and total cholesterol concentrations fall following exercise training. Variations in the effects on lipid concentrations following exercise training depend on the intensity of exercise performed and the gender of the study group (91). It was thought appropriate to examine changes in lipid profiles in a randomised controlled setting.

The following measurements were made: -

- Total cholesterol concentration

- HDL cholesterol concentration
- LDL cholesterol concentration
- Total/HDL cholesterol ratio

3.5.3 *Creatinine*

Serum creatinine was measured in most of the subjects for two reasons. Firstly to identify people with abnormal renal function who may have also had coexisting hypertension and thus altered cardiovascular function. Secondly, this value is necessary in order to compare high sensitivity C reactive protein levels, which were required for a study that was performed in parallel to the exercise training study and was co-ordinated by a different investigator.

Additional samples of blood to those used for the biochemical analysis described above were centrifuged for 10 minutes at 3000rpm and three tubes of serum and three tubes of plasma were obtained by pipetting the supernatant fluid. These samples were labelled with the subject's initials, study number, date on which the samples were collected and whether the sample was plasma or serum was also recorded. These tubes were placed inside a similarly labelled plastic bag, which was then stored at -70°C.

3.6 Results of screening

86 subjects were seen for an initial assessment including medical examination, ECG and transthoracic echocardiogram. 63 subjects were subsequently randomised to be included in the trial. The other 23 subjects were excluded for the reasons detailed in Table 1, Chapter 3.

Table 1 Chapter 3**Reasons for exclusion**

Reason for exclusion	Total number	Female	Male
Abnormal resting ECG	6	4	2
Abnormal ETT	7	3	4
Hypertension	2	0	2
Echo abnormality	3	0	3
Type 2 diabetes	1	1	0
Unwilling to be randomised	1	0	1
VO ₂ max test exceeds 43 ml/kg/min	2	0	2
Spouse	1	1	0
Total	23	9	14

(Where a subject had more than one exclusion criterion, the more clinically important one has been recorded.)

Abnormalities seen on the resting ECG included pathological q waves or left bundle branch block. Two of the subjects had a positive exercise treadmill test that suggested significant underlying coronary artery disease. They were subsequently investigated by coronary angiography and each was found to have severe triple vessel coronary artery disease. Another of the subjects developed left bundle branch block during the treadmill test that was rate related and not accompanied by symptoms or a change in blood pressure. This rate related left bundle branch block was thought to be due to hypertensive heart disease. Echo abnormalities included one subject with a small ventricular septal defect in the membranous septum. Although

small and clinically insignificant, this was thought to be potentially confounding with regard to intracardiac chamber pressures and wall motion and he was therefore excluded. Another subject had mild aortic regurgitation on echocardiography, which, whilst not clinically significant, was also thought to be potentially confounding. This subject also had mild mitral regurgitation and slight prolongation of the PR interval on the ECG, (0.22 sec). A third subject was found to have mild global impairment of left ventricular systolic function with an ejection fraction at the lower end of the normal range. This subject had no cardiovascular symptoms and went on to have a normal exercise tolerance test. He was reviewed six months later and had persisting mild global left ventricular systolic impairment without symptoms. One subject decided that, after successfully completing the screening tests, he did not want to be randomised as he intended to undergo a fitness program even if he was included in the control group. Altogether five subjects had a random glucose above the normal range on their initial test and went on to have a fasting sample taken. These were all within the normal range apart from one subject who had a raised fasting glucose and glycosylated haemoglobin level that was consistent with a diagnosis of type 2 diabetes.

3.6.1 *Excluded subjects*

The 23 subjects excluded represent 27 per cent of the population screened. This is consistent with published data suggesting that at least one third of asymptomatic older people have evidence of cardiovascular disease when screened non-invasively (123). 39% of the excluded subjects were women and 61% were men. This is also consistent with evidence that documents higher levels of cardiovascular disease in men compared to women in this age range and accounts for the slightly larger proportion of women compared to men who were included in the trial. The mean age

of the men excluded was 67.81 years, (range 61.5 – 77.17 years) and this was not significantly different to the mean age of the men who were included in the trial 66.26 years (range 60.42 – 79.42 years). The mean age of the women who were excluded was however significantly greater than those included in the study, 70.8, (range 62 – 79.5), vs. 67.29 years, (range 60.15 – 76.25), $p = 0.05$. This is likely to be due to the increasing prevalence of cardiovascular disease in older women with advancing age.

3.6.2 Conclusions

The importance of screening in studies involving older populations is highlighted by the results of this study where 27% of volunteers had evidence of cardiovascular abnormalities. Some of these volunteers may have decided to take part in this trial in order to receive a free cardiological assessment and they may have had symptoms prior to the study. However, the majority of excluded subjects were asymptomatic. As the screening investigations performed were not extensive, unrecognised coronary artery disease and hypertension could have been missed. The study findings must therefore be interpreted with this in mind (Appendix 2, Flow Diagram).

3.7 DEXA

Dual energy X-ray absorptiometry, (DEXA), is a non-invasive, highly reproducible and accurate technique that is usually used to measure bone mineral density but can also measure body composition (131). DEXA uses a three-compartment body composition model and assumes constant hydration of lean tissue (132). Although concerns have been raised regarding the accuracy of DEXA in measuring percentage fat in older populations (133), other authors conclude that it is able to detect small

changes in lean tissue mass in a group of individuals and is more accurate in this respect than densitometry (133).

3.7.1 *DEXA protocol*

Body composition was measured using a total body scanner Lunar DPX-L dual-energy, x-ray absorptiometer, (Lunar Corp, Madison WI; software version 1.3). This scanner uses a constant potential X-ray source and a cerium filter to produce two stable radiation beams. A series of transverse scans is made from head to toe at 1-cm intervals for a total scan time of approximately 15 minutes depending on height. When the two beams pass through the body, attenuation of the radiation depends on mass and tissue type. On the basis of regional attenuation, the total fat mass, total lean mass and lean mass of the arms and legs are calculated according to computer algorithms provided by the manufacturer, (Lunar Radiation Corp). Appendicular lean mass was calculated from the sum of the lean masses of arms and legs. Lean and fat masses were expressed as absolute values as well as a percent of total body weight. Fat free mass was the sum of all lean tissue and bone mineral but not fat mass. Bone mineral density was measured at the same time as body composition during the same scan. It was calculated from posterior-anterior scans of the lumbar spine, proximal femur and total body in each subject. The precision, (coefficient of variation of duplicate measurements in normal subjects) of these bone mineral density measurements in our laboratory are: - Total body bone mineral density, 0.4%; lumbar spine, 1.0%; femoral neck, 1.4%; Ward's triangle, 2.9%; trochanter, 1.6%; fat mass 2.7%; lean mass 0.8%. The scanner was calibrated daily against the standard calibration block provided by the manufacturer to control for possible baseline drift.

Each subject underwent DEXA scanning following randomisation. This occurred after the baseline fitness test had been completed but before commencing the exercise training program if they were in the exercise group. A second DEXA scan was performed after six months, or at the end of the study in all participants who had had an initial scan. Several subjects were unable to undergo DEXA scanning either because of logistic problems in arranging an appointment at the appropriate time or because they preferred not to have this test performed.

3.8 Applanation tonometry

Radial pulse wave analysis is a technique by which central haemodynamic parameters can be derived by mathematical transformation after registering a pulse wave format at a peripheral artery. High fidelity pressure contours can be obtained using applanation tonometry, which requires the flattening or applanation of the curved surface of a pressure containing structure. A surrogate pressure waveform representing the aortic root driving pressure can then be obtained via mathematical transformation of the waveform obtained via applanation tonometry of the peripheral artery (134), (Figure 3, Chapter 3). Comparisons between direct, (intravascular) and indirect, (applanation tonometry) recordings of arterial pressure in humans and animals have demonstrated excellent correlation between the harmonic components of the simultaneously acquired invasive and non-invasive contours (6). Applanation tonometry thus provides a high fidelity recording of arterial pressure waveforms. Intraobserver variability and reproducibility of this technique have been shown to be similar to that for the recording of systemic blood pressure (135) but despite its apparent precision, this technique is not yet widely used in clinical practice.

3.8.1 *Augmentation index*

The shoulder of the pressure wave is defined as the first concavity on the upstroke of the wave and separates the initial pressure rise from that later in systole, (P1) and is caused by left ventricular ejection. The late systolic pressure peak, (P2) is thought to result from early-reflected pressure waves from the peripheral circulation. The height and timing of this secondary pressure wave are dependent on the degree of arterial wall stiffening. The central augmentation pressure is the difference in height between P1 and P2. The augmentation index is the height from the shoulder to the peak of each averaged pressure waveform divided by the total height from foot to peak expressed as a percentage, i.e. the central augmentation pressure divided by the pulse height, (Figure 3, Chapter 3). The augmentation index thus characterizes the pressure wave reflection and is an indicator of arterial stiffness. A 15-fold increase in the augmentation index of the carotid artery waveform has previously been noted between the first and eighth decades (136). This is a far greater increase than that observed in systolic blood pressure with increasing age. Augmentation indices have also been found to be lower in athletes compared to age-matched sedentary people (6). Exercise training has been found to increase arterial compliance and reduce arterial stiffness independent of changes in blood pressure in a small, non-randomised study (134, 137) and has also been shown to be related to levels of physical activity and measures of fitness such as VO_2max (6). Applanation tonometry can be used in conjunction with data from Doppler recordings of aortic blood flow to estimate aortic compliance and stiffness. Measurement of aortic blood flow was not performed on all subjects in this study so that in this study arterial compliance can only be deduced from measurements of augmentation index.

3.8.2 *Obtaining a recording*

A micro-tip SPT-301 pencil-type transducer was placed over the maximal pulsation of the right radial artery and its angulation and position on the skin altered slightly whilst applying some downward pressure. Once the manometer was directly over the artery, high amplitude peaks were seen on the pressure waveform. With minimal practice, good quality, reproducible signals were easily obtained. A minimum of 20 seconds of waveform data were recorded as direct analogue-to-digital conversions and stored on disc with an IBM model 30 computer. Specifically designed software identified the start-systolic point and the end-diastolic point on the pressure waveform. The software also assigned measured systolic pressure to the peak of the waveform and measured diastolic pressure to the end-diastolic point on the waveform. All measurements were made with the subjects sitting after a 15-minute rest. Blood pressures were obtained twice from the left brachial artery using a standard sphygmomanometer and the mean of the two values recorded.

3.9 *Quality of life*

As well as the benefits on health and disease, physical activity is also thought to relieve symptoms of depression and anxiety, improve mood and improve health-related quality of life by enhanced psychological well being and improved physical functioning in persons compromised by poor health (138, 139). Quality of life was therefore assessed at the beginning and at the end of the six month study for subjects in both groups to identify improvements in quality of life related to exercise training. The Medical Outcomes Study, MOS 36-Item Short Form 36, (SF-36) is a general health status questionnaire developed in the USA and subsequently validated for use in other populations. It can be completed in less than 10 minutes and is a general rather than a specific outcome measure. As a generic questionnaire, it can compare

health status before and after an intervention in the same population. The SF36 uses eight health scales to measure three aspects of health; - functional status, well being and overall evaluation of health. It measures health-related quality of life classified by eight dimensions, namely, physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, pain, vitality and general health perception. The responses to the questions are summed to provide eight scores between 0 and 100. This questionnaire has been shown to be a valid measure of perceived health, is acceptable to patients and is internally consistent (140). Recent studies have identified variations in data quality and the resulting scores when this questionnaire is administered in different ways i.e. postal questionnaire versus supervised interview. The questionnaire was therefore used in a consistent way throughout this study. Supervised interviews result in higher response rates and fewer missing data (141), however they require an additional amount of time to be spent at the hospital or exercise training facility. In addition, clinic based interviews have been shown to exaggerate health status compared with self-assessment (141). The questionnaires were therefore given to each participant immediately after their echocardiogram had been completed. They were then asked to return the completed questionnaire when they attended for their exercise stress test or VO₂max test. This allowed participants to highlight questions they were unsure of. When completing the final questionnaire, the participants did not have access to their baseline questionnaire. One concern regarding the use of this questionnaire was its validity in a healthy population and whether the volunteers in this study would have scope in their perceived level of fitness and health in which to change over a six month period.

3.10 Physical activity questionnaire

An assessment of the amount of regular physical activity performed by each subject was made by asking all participants to complete a physical activity questionnaire at the beginning and the end of the study. This was particularly important for subjects in the control group in order to verify that these participants had not significantly increased their habitual activity levels over the course of the trial. Participants completed the questionnaires at home in order to minimize the amount of time spent at hospital visits and thus maximize subject compliance and attendance at end of study appointments. However, some of the participants were unclear as to the meaning of several questions. It also became apparent, after the study had finished, that some of the participants in the exercise group had not included their exercise training as part of their weekly activity in the end of study questionnaire. In retrospect, the quality of information gathered from the physical activity questionnaires may have suffered and could have been improved by supervising the questionnaires more closely.

3.10.1 Nurses health study questionnaire

Ideally, a physical activity assessment tool should be reliable and valid, sensitive to change in individual activity patterns and easy to administer. Although many measures of physical activity have been constructed, few are simple, short and appropriate for self-administration. The Nurses Health Study is a study that assessed the reproducibility and validity of a self-administered physical activity questionnaire in 116 680 female nurses (142). They found that a simple questionnaire on activity and inactivity was reasonably valid. Other studies have used the Stanford seven day activities recall questionnaire, which is similar to the Nurses Health study in that it assesses both the duration and intensity of physical activity. The Stanford seven day

physical activities recall questionnaire also provides useful estimates of habitual exercise (143) however, it was felt that, for our study, the Nurses Health questionnaire was simpler and thus easier to administer. The Nurses Health Study questionnaire is a self-reported measure of average weekly recreational physical activity, estimated for the past six months or the past year. It includes information regarding eight moderate or vigorous activities, as well as the number of flights of stairs climbed per day (142). In addition, the usual walking pace and information regarding four sedentary activities is recorded on a separate grid. A copy of the questionnaire given to each participant is provided see Appendix 3. The workload, expressed as the number of metabolic equivalents, (METs) required per hour to perform an activity defined its intensity. Workloads for specific activities were obtained from a paper reporting the usefulness of the Nurses Health Study questionnaire (142). For each activity, the number of hours spent performing the activity per week was multiplied by a MET level in order to obtain an activity score. Activity scores for each of the eight activities plus the energy used in climbing flights of stairs were then added together to give weekly energy expenditures for all activities. Inactivity scores were calculated in a similar way and the scores for each of the four sedentary activities were added together. Because previous studies have suggested that scores of sedentary behaviour are relatively invalid, this value was recorded and analysed separately (142). The ratios of weekly activity versus weekly inactivity scores were also noted. In this way, variations in the way that individuals assessed their weekly activity and inactivity could be standardised, (Appendix 3).

3.11 Maximal exercise capacity, (VO_2max)

The amount of oxygen used by the body during peak exercise, VO_2max , is considered to be the best index of aerobic capacity and cardio-respiratory function.

Whilst it can be estimated using formulas that calculate values from the amount of work performed during maximum exercise, these are limited by physiological and methodological inaccuracies and direct measurement is therefore preferred (125). Direct measurement uses analysis of inspired and expired gas, which produces reliable and reproducible measurements, giving the most accurate assessment of functional capacity (125).

3.11.1 *VO₂max Protocol*

If a subject successfully completed all the screening tests, their maximum aerobic capacity, (VO₂max) was assessed by walking or running to exhaustion on a treadmill approximately one week after the exercise stress test. Each subject was instructed to refrain from drinking alcohol or caffeine containing drinks for 12 hours and from eating for three hours prior to the test. In addition, no strenuous exercise should have been performed within the previous 24 hours. Between 60 and 120 minutes prior to exercising, subjects were instructed to consume 500ml of water to standardise hydration. Weight, resting blood pressure and resting heart rate were recorded while the researcher acquainted the subject with the testing protocol. Each protocol was based on the individual's Bruce protocol exercise test performed earlier. Before the test, the subject was fitted with a mask with breathing valve and supportive headgear as well as a heart rate monitor. Careful attention was made to close fitting of the mask in order to avoid air leakage during the test. After a warm-up period on the treadmill, lasting approximately five minutes followed by stretching exercises, the exercise protocol was begun at an initial workload calculated in metabolic equivalents (METs) of approximately 60% of age predicted maximum heart rate. Successive one-minute stages increased workload by 1.0 or 1.5 METs until exhaustion, depending on the subjects' fitness level. Test termination for reasons

other than exhaustion was carefully documented. This protocol, customised for each subject, lasted between six and 12 minutes. During the test, heart rate was monitored continuously and recorded every 30 seconds. Respiratory gas exchange variables were acquired and analysed every 15 seconds using a Schiller CS-100 metabolic analyser. The speed and inclination of the treadmill at each stage of the test was also recorded. The presence of musculoskeletal problems was noted in addition to other information such as whether the subject was walking or running or holding onto the handrail as these factors all effect the final VO_2max value. At test termination, subjects were warmed down on the treadmill for five minutes. Immediately before and after every test the machine was calibrated to ensure no drift in calculated values for gas volume and concentration had occurred. Only where calibration values were acceptable according to an automatic program was it possible to perform the test using the gas analysis machine. If calibrated values differed by more than 5% between pre and post test readings the test was repeated.

3.11.2 *Analysis of gases*

The measurement of gas exchange variables can be performed using rapid gas analysis for oxygen and carbon dioxide and computerised by on-line analysis systems. However, gas exchange measurement systems are costly and require meticulous maintenance and calibration for optimal use. Personnel who administer these tests must therefore be trained and proficient in this technique. Data collected by the metabolic analyser included ventilatory volume, (L/min), oxygen uptake, VO_2 (L/min and ml/kg/min), carbon dioxide output, VCO_2 (L/min), respiratory quotient, (RQ) and ventilatory or anaerobic threshold. The respiratory exchange ratio, (RER) partly reflects the predominant fuel that is used for cellular metabolism and represents the amount of carbon dioxide produced, divided by the amount of oxygen

consumed. This value generally ranges from 0.7 to 0.85 at rest but at high levels of exercise, carbon dioxide production exceeds oxygen consumption and the RER therefore rises to a value above 1.0. Thus, an RER greater than 1.0 usually indicates that the subject is giving maximum effort.

3.11.3 *Determining true max*

Maximum oxygen uptake, VO₂max, is defined as the point at which no further increase in measured VO₂ occurs despite an increase in work rate. A plateau in VO₂ with increasing workload, a respiratory quotient of 1.1 or greater, and the achievement of maximum age-predicted heart rate can all be used to determine true “max”. In this study, at least two of these three measures were required for true max to be recorded. This is in accordance with other studies that have measured VO₂max in older people and is more accurate than depending on a plateau in VO₂ alone. The mean of the two highest values recorded was taken to be VO₂max for all tests where the RER exceeded 1.1. Normal values for VO₂ max are detailed below.

Table 2 Chapter 3
Normal exercise capacity values in older men and women

Age	Men VO ₂ max (ml/kg/min)	Women VO ₂ max (ml/kg/min)
60-69 years	33 ± 7.3	27 ± 4.7
	9 METS	8 METS
70 – 79 years	29 ± 7.3	27 ± 5.8
	8 METS	8 METS

An identical test was performed on all randomised subjects at the end of the six months study duration. Thus, each subject had a fitness evaluation at the beginning and also at the end of the study. It was not possible to perform the second test using personnel who were blinded to the subjects “treatment” group. However, because the same personnel performed all of the tests, any variations in VO₂max results arising from changes in protocol or attitude were minimised. During the second test, the results of the baseline VO₂max test were not available to the staff members so that they could not be influenced to give extra encouragement to the subject or allow them to stop earlier than necessary.

3.11.4 *Repeated tests*

Several of the initial tests and two of the end of study tests were repeated because it was apparent that the initial test results were inadequate or suggested machine error or mask leakage. Two of the initial tests were repeated when it became apparent that the subjects had breathed solely through their nose throughout the entire test.

3.11.5 *Additional data*

In addition to the data collected and recorded above, some extra information regarding exercise haemodynamics was recorded.

Time to 90% maximum heart rate

Predicted maximum heart rate for age is calculated by subtracting the subject’s age from 220. 90% of this figure is therefore 90% maximum heart rate. The time taken to reach this heart rate during the VO₂max test was recorded.

Maximum workload

Maximum METS, or the maximum workload achieved by the subject whilst performing the VO₂max test was calculated by the following equations using the speed and inclination of the treadmill when the subject had reached maximum effort. For subjects who were walking, the following calculation was used to calculate expected VO₂max and this value was divided by 3.5 to acquire maximum METS values.

$$\begin{aligned}\text{VO}_2 \text{ (ml/kg/min)} &= \text{horizontal component} + \text{vertical component} + \text{resting component} \\ &= (\text{Speed (m/min)} \times 0.1) + (\text{gradient} \times \text{speed (m/min)}) \times 1.8 + 3.5 \\ &= (\text{Speed (km/h)} \times 16.67) \times 0.1 + (\text{gradient} \times (\text{speed (km/h)} \times 16.67)) \times 1.8 + 3.5 \\ \text{METS} &= \text{VO}_2 \text{ (ml/kg/min)} / 3.5\end{aligned}$$

For subjects who were running at peak exercise the following calculation was used to calculate expected VO₂max and this value was divided by 3.5.

$$\begin{aligned}\text{VO}_2 \text{ (ml/kg/min)} &= \text{horizontal component} + \text{vertical component} + \text{resting component} \\ &= \text{Speed (m/min)} \times 0.2 + (\text{gradient} \times \text{speed (m/min)}) \times 0.9 + 3.5 \\ &= (\text{Speed (km/h)} \times 16.67) \times 0.2 + (\text{gradient} \times (\text{speed (km/h)} \times 16.67)) \times 0.9 + 3.5\end{aligned}$$

In these equations, gradient is expressed as a fraction i.e. 4% = 0.04.

Anaerobic threshold

The anaerobic threshold was calculated automatically by the gas analyser and presented in the computer read out of gas analysis results.

3.12 Randomisation

Those subjects who satisfied the inclusion criteria, did not meet any of the exclusion criteria and had also completed a baseline VO₂max test, were sequentially randomised to an intervention or control group according to a prepared randomisation schedule. The randomisation schedule was prepared using a computer software package, Windows Excel '97. To ensure a balanced design, in the event that the study failed to recruit the full complement of subjects, randomisation was balanced within each successive block of six subjects. Within a block, a pseudorandom number was generated and then ranked. The three with the lowest random number were allocated to the intervention group. The three with the highest random number were allocated to the control group. Randomisation was performed independently by the bio-statistician in the cardiovascular research department. Subjects were told which group that they had been randomised to in person by the principal investigator. Once randomisation had been performed, the group into which a subject was placed was not changed.

3.13 Exercise intervention

All exercise tests and training sessions were conducted at the Unisport Training centre, University of Auckland, Auckland, New Zealand. In the event of medical emergency, this facility is equipped with emergency medical equipment and all staff are trained in cardiopulmonary resuscitation. In addition, physicians were on site (60 meters away) during all training sessions. Trained exercise physiologists who had a

background in exercise prescription for special populations staffed each session. A staff to subject ratio of 1:8 or lower was maintained at all times to assure that each subject was carefully monitored and that their exercise goals were achieved throughout the six month training protocol.

The training protocol was a two-phase exercise program, designed to ensure that the desired improvements in aerobic capacity occurred with minimal injury and maximal compliance. Subjects were involved in three supervised exercise sessions per week, each lasting one hour, as well as one unsupervised exercise session per week. Prior to the exercise program, subjects performed a warm-up for a minimum of five minutes followed by a five-minute stretching program. Once these had been completed, subjects began their exercise program, which was prescribed daily by an exercise physiologist trained in exercise prescription for older people.

Stage one of the training protocol was completed during the first two to four weeks of training. During this stage, exercise duration and intensity were increased at an accelerated rate with the goal of having subjects achieve 45 minutes of continuous exercise at prescribed training intensity. Initial workloads were 30 minutes at an exercise intensity approximating 50% VO_2max , based on their pre-training exercise test. Once the prescribed exercise was comfortably completed with an appropriate haemodynamic response, (measured by exercise heart rates and blood pressures), the subjects' exercise prescription increased in duration, (five minutes) and/or intensity, (5% VO_2max) until the subject was training for 45 minutes at a target heart rate achieved at 70% VO_2max on their pre-training exercise test, (stage two). In this way, relative training intensity remained the same throughout the second stage of the training program while absolute exercise intensity was allowed to change. Previous

studies using similar regimens have been able to show changes in VO_2max of 19% after six months (46).

During training sessions, endurance exercise consisted of walking, jogging or stationary cycling. Subjects resting heart rate, exercise workload, mode of exercise, and session comments were recorded and the use of heart rate monitors ensured that all exercise modalities were carried out at the appropriate aerobic intensity. Exercise prescriptions were also adapted to assure that subjects continued to train appropriately or to take account of injuries or illness. The use of different training modalities introduced differences in peripheral adaptation, (different muscle groups), however central adaptations should have been unaffected due to the use of a carefully monitored training heart rate range. The advantage of multiple modalities is improved subject compliance, which is important over the course of such a long training program. The fourth training session per week was unsupervised and in order to ensure that appropriate levels of activity were achieved during this session, the heart rate monitor was worn for this session also.

3.14 Power calculation

The study was powered, ($1 - \beta = 80\%$ at the 5% significance level) to primarily identify a difference in tissue Doppler imaging parameters. At the time when the study was designed no papers had published reference values for E' in master athletes. However, studies using Doppler transmitral flow velocities suggested that the expected pattern of diastolic alterations normally seen in response to age is modified in the older athlete (82). Tissue Doppler imaging had been used to assess myocardial velocity gradients from the posterior wall of the left ventricle in both athletes and age-matched sedentary controls (85). This study showed that athletes

had values 42% greater than age-matched sedentary controls (85). Values for E' in normal individuals have been published by a variety of authors. Values differ depending on the site at which the annular velocity has been measured and they are higher in the lateral compared to the septal annulus (144). It is now generally accepted that E' i.e. the velocity of the mitral annulus during early left ventricular filling, is greater than 8 cm/s in normal individuals (34). Older people with delayed relaxation have values below 8 cm/s (34). Sohn et al have published values for E' in different age groups (32) and these are detailed in the following table.

Table 3 Chapter 3

Mitral annular velocity according to age

Age	20-29	30-39	40-49	50-59	60-69
(years)	n=12	n=12	n=12	n=12	n=12
E/A	1.9 (0.4)	1.7 (0.4)	1.4 (0.4)	1.3 (0.3)	1.0 (0.2)
E' (cm/sec)	11.8 (1.4)	13 (1.9)	9.2 (1.4)	8.5 (1.9)	7.5 (1.6)
E'/A'	1.4 (0.2)	1.5 (0.5)	1.0 (0.2)	0.8 (0.2)	0.7 (0.1)

(32)

The technical success rate of measuring tissue Doppler velocities has been shown to be high, 94%, which compares favourably with success rates of 73% and 61% for pulmonary vein flows and Valsalva manoeuvre respectively (122). They can be successfully performed in the vast majority of subjects even when two-dimensional images are of poor quality. Using the above measures and assumptions about the likely direction of change, an expected change, equal to a reversal of age related changes of 10 years i.e. a change in E' of approximately 1.1cm/s (32), was chosen. Assuming high reproducibility rates for E', it was felt that these changes could be detected using a minimum number of 30 subjects in each group. It was initially assumed that 15% of subjects would drop out in each group, resulting in a reduction

in the degree of sensitivity to change and thus a change of 1.5cm/s could be identified.

Because of cost restrictions associated with performing and analysing MRI images, fewer subjects in each group were randomly allocated an MRI scan at baseline and six months. Studies using MRI have shown that groups as small as five are large enough to identify significant changes in left ventricular mass and volumes (75). Because of this uncertainty regarding the degree of cardiac change that could be expected, the largest number of subjects possible within the cost constraints of this study was chosen.

3.14.1 *End-points*

A between group comparison of baseline versus end of study values for the following: -

Primary end points

- a) The change in myocardial velocity during early left ventricular filling, (E')
measured using tissue Doppler imaging at the septal aspect of the mitral annulus
- b) The change in the ratio E/E'

Secondary end-points: -

Echocardiography

- a) Change in mitral annular velocity during late left ventricular filling, A'
- b) Change in the ratio E'/A' using tissue Doppler imaging
- c) Change in the ratio E/A using Doppler transmitral flow velocities
- d) Change in the deceleration time of the E wave using Doppler transmitral flow velocities

MRI

- a) Change in left ventricular end diastolic and end systolic volumes (LVEDV, LVESV)
- b) Change in left ventricular mass

Exercise capacity

- a) Change in VO_2max
- b) Change in resting heart rate and blood pressure

Tertiary end points

Changes in quality of life, arterial compliance, lipid concentration and body composition.

3.15 Statistical analysis

Continuous, normal endpoint data were analysed on an intention-to-treat principle and subjects who dropped-out of either treatment group were encouraged to provide endpoint data. Missing at random data were imputed using maximum likelihood estimation within the mixed procedure of SAS. A mixed models approach to repeated measures was adopted to examine differences between treatment groups over time. This approach is robust to departures from sphericity and permits data from all subjects to be used. Significant main and interaction effects were tested using orthogonal contrasts. Should the groups be confounded, analysis of covariance in a mixed model was used to provide appropriate adjustments. All tests were two tailed and a 5% significance level was maintained throughout. An analysis of completers focused on the difference in E' between six months and baseline and was compared using Student's t-test for independent groups. Comparison between responses in tissue Doppler and MRI and between each modality and other clinical

outcome variables was made in univariate models using Spearman's correlation coefficients and in multivariate models using a variety of iterative linear and logistic regression techniques.

3.16 Compliance

Staff prescribing the individual exercise training protocols collected compliance data for all subjects participating in the exercise training. Three of the four sessions per week were supervised and subjects were required to attend the exercise-training gymnasium during session times, which were from 6am until 10 am on Monday, Wednesday and Friday mornings. These times allowed subjects who were working full time to attend training sessions before work, whilst still allowing retired participants the option of attending the gym at times that avoided the morning rush hour. For the fourth unsupervised session, the gym was made available at weekends and on a Tuesday morning, free of charge, to the participants. Alternatively, participants were encouraged to wear heart rate monitors during weekend activities such as lawn mowing or walking. Staff at the training centre asked each participant whether they had been able to complete this session each week. Thus this information may not have been as reliable as that gathered during supervised sessions.

Before inclusion into the study, potential participants were told that the trial would require regular attendance at the training facility for a six month period. This meant that people who were planning to make long trips overseas were not included in the trial. One subject did go abroad for a 15-week period and restarted exercise training on her return. Unfortunately she subsequently required an abdominal operation and

was unable to complete the last four weeks of the exercise training or the end of study fitness test.

Several subjects contracted the 'flu towards the end of the training period and stopped exercising for approximately three weeks before they were well enough to restart training. Where this period of ill health occurred in the last month of the training program the training period was extended by two to four weeks in order for the subject to fully recover to their pre-morbid fitness level before end of study evaluation was performed.

3.16.1 *Injuries*

Subjects reported injuries sustained during the exercise-training period to staff at the training facility. Thus, far more information regarding injuries was available for the training group compared to the control group who were not specifically questioned regarding injuries over the six month period. Some of the injuries sustained in the exercise group lead them to discontinue the exercise-training program for variable periods of time. Most injuries were sustained at the weekend when performing activities not related to the exercise-training program rather than during training.

Figure 1 Chapter 3

Tissue Doppler measures of mitral annular velocities

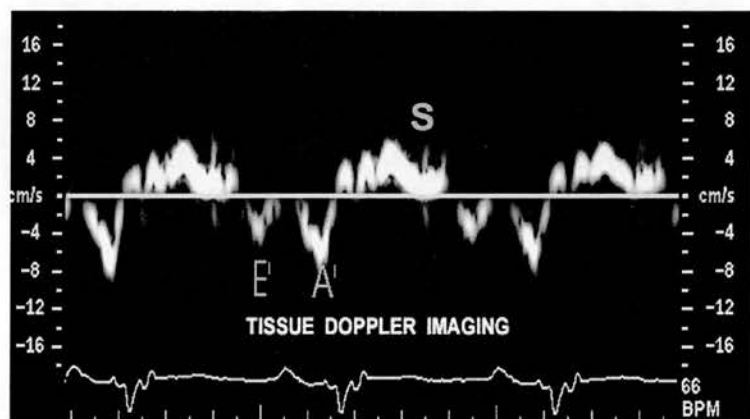


Figure 2 Chapter 3

Doppler transmitral flow velocity measurements

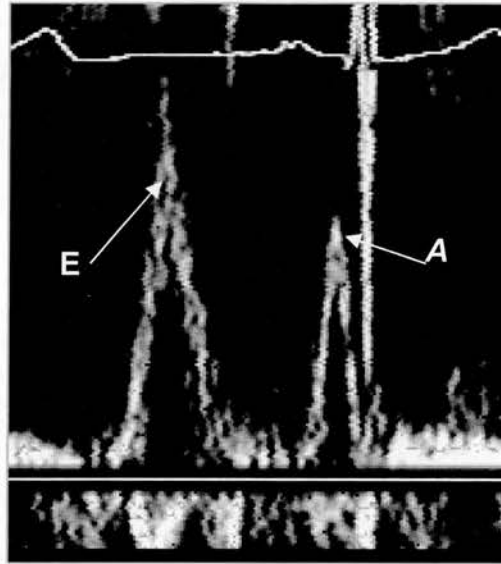
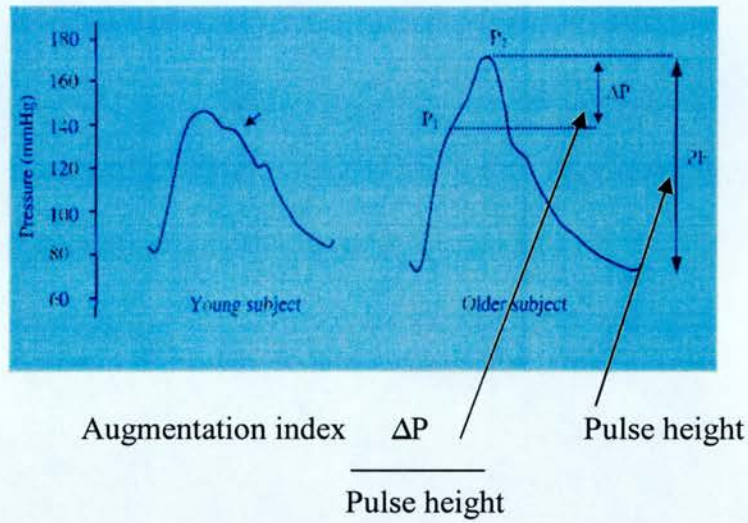


Figure 3 Chapter 3

Augmentation index



ΔP = central augmentation pressure

Table 4 Chapter 3

Previous studies of exercise training

Author	No	RCT	Control Group	Age	Gender	Exercise Duration	↑ VO ₂ max	↓ HR	↓ Bp
Shapiro	15	No	No	18-49	Male	6 weeks	14%	No	No
McGuire	5	No	No	50-51	Male	6 months	18%	14%	Yes
Kasch	15	No	No	45	Male	33 years		No	No
Sadaniantz	16	No	Yes	32-46	Male	1 year	27%	Yes	No
Ehsani	10	No	No	61-67	Male	11 months	23%	Yes	No
Spina '97	8	No	No	63-67	Male	9 months	29%	Yes	No
Spina '98	10	No	No	64-66	Male	9 months	22%		No
Spina '93	31	No	No	60-66	Male/ Female	9-12 months	19-22%	Yes	Yes
Spina 2000	10	No	No	64-66	Female	9 months	23%	No	
Kohrt	110	No	No	60-71	Male/ Female	9-12 months	12-36%	Yes	
Seals	11	No	No	61-65	Male/ Female	6 months low intensity	12%	No	Yes
Seals	11	No	No	61-65	Male/ Female	6 months high intensity	18%	Yes	Yes
Stratton	13	No	No	60-82	Male	6 months	21%	Yes	Yes
Stratton	11	No	No	24-32	Male	6 months	17%		Yes
Schulman	10	No	No	59-61	Male	6-8 months		Yes	Yes
Levy	13	No	No	60-82	Male	6 months	19%	Yes	No
Levy	11	No	No	24-32	Male	6 months	19%		
Parkari	110	No	Yes	45-65	Male	5 months	None		No
Morrison	32	Yes	Yes	51	Female		13%	No	Yes
Hagberg	59	Yes	Yes	70-79	Male/ Female	6 months	22%	Yes	No

Chapter 4

Exercise Training in Older Men and Women Improves Exercise Capacity without Significantly Altering Haemodynamic Parameters or Arterial Compliance

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Exercise Training in Older Men and Women Improves Exercise Capacity without Significantly Altering Haemodynamic Parameters or Arterial Compliance

4.1 Introduction

Aging is characterised by a progressive decline in maximal aerobic exercise capacity, an increase in resting blood pressure and an increase in arterial stiffness (136). These changes are generally attributed to age-related changes in skeletal muscle and the cardiovascular system as well as the adoption of a more sedentary life-style. Exercise training can result in substantial improvements in exercise capacity in older adults (28), but the effects of brief episodes of exercise training on arterial stiffness and haemodynamic parameters such as resting heart rate and blood pressure in this age group are conflicting, (Table 4, Chapter 3). Almost all of the studies of exercise training in older people have been non-randomised, used small numbers of participants or only included men. Evidence documenting the impact of exercise training in older people on other significant risk factors for cardiovascular disease such as aortic compliance is also limited. Several cross-sectional studies suggest that increased aortic compliance accompanies increased physical activity (6, 134, 145). However, the impact of exercise training on arterial compliance in previously sedentary older people has been reported in only one non-randomised study which identified a significant increase in arterial compliance following exercise training (137).

This chapter describes the changes in arterial compliance, resting haemodynamic variables and exercise capacity in men and women aged 60-79 years who were

randomly assigned to six months of exercise training or remained sedentary for the same period.

4.2 Methods

These are described in detail in Chapter 3. Central augmentation index is a measure of arterial compliance and can be calculated by dividing the pressure peak caused by pulse wave reflection by the pressure peak caused by ventricular ejection. The data were analysed on an intention to treat basis.

4.3 Results

4.3.1 Study participants

86 volunteers underwent screening and 63 of them were randomised into the study. (See results of screening, Chapter 3). There were 31 participants in the control, (sedentary) and 32 in the intervention, (exercise) group and 57% of participants were female. The mean age of the group was 67 years, range 60-79 years, (Table 1, Chapter 4). All but two of the subjects were Caucasian. Two men in the intervention group were of Indian and Iranian origin. Only two participants were current smokers and each smoked less than one cigarette per day. 38% of the participants were ex smokers, 13 in the control and 11 in the intervention group. The mean time since stopping smoking was 23 years, range 0 - 46 years. 84% of the participants drank alcohol but mean consumption was only 5.8 units per week, range 1 – 18 units per week and the mean alcohol consumption in each group was not significantly different.

4.3.2 *Baseline parameters*

Mean VO_2max was 27.35 ± 6.79 ml/kg/min for the study population as a whole at the beginning of the trial. No significant differences in baseline parameters between the control and intervention groups were identified except that resting heart rate was faster and maximal exercise capacity, (VO_2max) was lower in the intervention compared to the control group at baseline, (Table 1, Chapter 4). Other measures of exercise capacity such as anaerobic threshold and maximum workload at baseline were greater at baseline in the control compared to the intervention group but these differences did not reach statistical significance, (Table 1, Chapter 4). When female participants were analysed separately, the difference in baseline exercise capacity between the groups was still present, however the difference in baseline exercise capacity disappeared when male participants were analysed separately, (Table 2, Chapter 4).

4.3.3 *Compliance*

84% of participants in the intervention group successfully completed the six month exercise training program. 68% of these had attendance rates at the exercise training sessions of 65% or greater, averaged over the six month period. Four subjects in the intervention group completed less than one month of exercise training and a fifth trained for three months before illness and social commitments caused her to discontinue training. All of these participants were female and all provided end of study data. The mean VO_2max of these five participants at baseline was 24.8 ml/kg/min and after six months it had fallen to 23.98 ml/kg/min. Despite being in the control group, one subject significantly increased his weekly physical activity during the study period. He began training for a half marathon and increased his VO_2max from 44.3 ml/kg/min at baseline to 51.75 ml/kg/min after six months. As the trial

data were analysed on an intention to treat basis, all of the above subjects were included in the final study analysis.

4.3.4 *Changes in exercise parameters*

Despite the drop out rate of 15.6% described above, a significant improvement in exercise capacity was seen in the intervention compared to the control group. The intervention group increased its exercise capacity by 4.31 ± 4.7 ml/kg/min, from 26.46 ± 5.4 to 30.72 ± 6.53 ml/kg/min, which constitutes a mean increase of 16.1%. In the control group, initial values were 29.87 ± 6.7 ml/kg/min at baseline and 28.77 ± 7.46 ml/kg/min after six months, which constitutes a mean reduction of 3.68% in exercise capacity, (Table 3, Chapter 4). Exercise capacity in the intervention group therefore showed a net increase of 19.78%. Other parameters that measure exercise capacity such as maximum workload achieved at peak exercise and anaerobic threshold also showed significantly greater improvements in the intervention compared to the control group following exercise training, (Table 3, Chapter 4). The respiratory exchange ratio during the VO_2max test was 1.22 ± 0.1 in the control and 1.21 ± 0.12 in the intervention group before exercise training and 1.19 ± 0.11 and 1.19 ± 0.08 respectively in the groups at the end of the study. These values indicate that the subjects in both groups attained true maximal exercise capacity during the VO_2max tests.

4.3.5 *Heart rate*

There was a reduction in resting heart rate when comparing baseline to end of study values in both groups. This reduction was larger in the intervention compared to the control group, however, the change in resting heart rate was not significantly

different between the two groups, $p = 0.19$, (Table 4, Chapter 4). There was a greater prolongation of the PR interval on the ECG in the intervention group compared to the control group, a change that would normally accompany a slower resting heart rate. The difference in the change in PR interval between the groups was significant, $p=0.02$, (Table 4, Chapter 4). Peak heart rate during exercise did not change significantly in the intervention compared to the control group although there was a trend towards a greater reduction in peak heart rate in the control compared to the intervention group.

4.3.6 *Blood pressure*

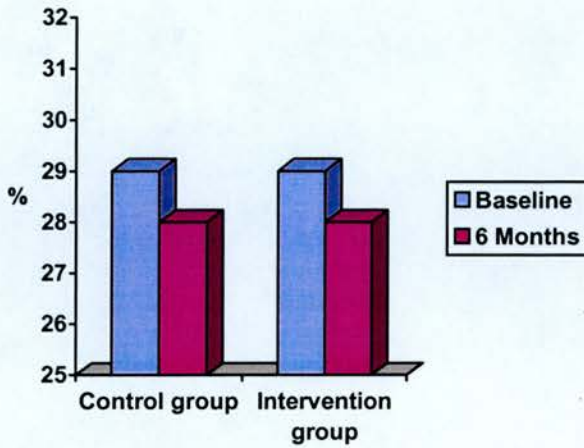
Both groups showed a small reduction in resting systolic blood pressure when comparing baseline to end of study recordings. Although there was a trend towards a greater reduction in both systolic and diastolic blood pressure in the intervention compared to the control group, the change in blood pressure over the six month period was not significantly different when comparing the two groups, (Table 4, Chapter 4).

4.3.7 *Applanation tonometry*

Baseline values for central augmentation index were consistent with those published in an age-matched population (136), $26 \pm 9\%$. Both groups showed a slight reduction in mean central augmentation index over the six month period but the change in central augmentation index was not significantly different between the two groups, control group, $-1.1 \pm 13\%$ vs. intervention group, $-0.8 \pm 8.1\%$, $p = 0.93$, (Figure 1, Chapter 4). Systemic vascular resistance decreased more in the intervention compared to the control group but this difference was not significant, (Table 5, Chapter 4).

Figure 1 Chapter 4

Change in central augmentation index



4.4 Discussion

4.4.1 Exercise capacity

Baseline measures of exercise capacity were consistent with those published previously for sedentary older people (52), confirming the subjects to be representative of a sedentary older population, (Table 6, Chapter 4).

Table 6 Chapter 4

Exercise capacity in older adults: reference values

Age	Men VO ₂ max (ml/kg/min)	Maximum Workload (METS)	Women VO ₂ max (ml/kg/min)	Maximum workload (METS)
60 - 69 years	33 ± 7.3	9	27 ± 4.7	8
70 - 79 years	29 ± 7.3	8	27 ± 5.8	8
(This study) 60 - 79 years	30.3 ± 5.8	10	26.2 ± 5.5	9

(52)

The baseline difference in exercise capacity between the intervention and control groups in this study may have been due to the slightly larger number of women in the intervention compared to the control group. As women tend to have lower values for VO_2max compared to men, this initial difference may have had an impact on the trial results. A group that is less fit to start with may achieve greater benefit from exercise than one that is fitter initially. However, previous studies suggest that women tend to increase exercise capacity to a lesser degree than age-matched men following exercise training (89), which makes the substantial increase in exercise capacity seen in the intervention group of additional significance.

This randomised controlled trial confirms the ability of older people to improve exercise capacity significantly and by a magnitude that is similar to that seen in younger populations (47). Non-randomised trials of exercise training in older people have reported improvements in VO_2max of between 12 and 24% (89), (Table 4, Chapter 3). In our study an absolute increase of 16.1% and a relative increase of 19.8% compared to the control group was achieved despite a drop out rate of 16% in the intervention group. Significant improvements in exercise capacity were also seen when VO_2max was normalised to fat free mass, which suggests that a change in weight was not wholly responsible for the improvement in exercise capacity in the intervention group, but that significant increases in fitness were achieved.

4.4.2 *Change in heart rate*

Resting bradycardia is generally thought to accompany improvements in fitness. Observational studies have identified slower resting heart rates in older athletes compared to age-matched sedentary peers (63, 81, 82) and animal studies and small, non-randomised trials of exercise training in older people have identified a lowering

of resting heart rate of as much as 14% following exercise training, (62, 68, 70, 76, 146), (Table 4, Chapter 3). However, not all studies have reported a significant slowing of heart rate following exercise training, particularly those that have included control groups (89, 94). In our study, despite the inclusion of moderately large numbers of participants and a 16% increase in VO_2max in the intervention group, no significant difference in the change in heart rate between the control and intervention groups was seen. The lack of significant change in heart rate in this study is unlikely to be due to an inadequate exercise regimen. Measurement of resting heart rate under standard conditions as well as the presence of a control group reduced observer bias and reduced the chance of reporting a slowing of heart rate with exercise training because this was an expected or assumed finding. However, a significant prolongation of the PR interval on the resting 12 lead ECG was seen in the intervention compared to the control group. This ECG parameter would be expected to lengthen with slower heart rates and provides indirect evidence to support the heart rate lowering effect of exercise training in older people. Significant shortening of the PR interval has previously been observed following detraining in young, elite athletes (147). These results suggest a trend towards a lower resting heart rate following increased physical activity. A larger study, or one that used a more prolonged exercise training regimen may have identified a significant difference in the change in resting heart rates between the two groups. Peak heart rate during exercise also showed no significant change in either group over the six month trial period. This lack of training effect on peak exercise heart rate has previously been reported from other trials of exercise training as well as in observational studies in athletes (76, 77).

4.4.3 *Change in blood pressure*

The trend towards a greater reduction in blood pressure in the intervention compared to the control group is in agreement with large epidemiological observational studies that identify lower resting blood pressures in active populations and athletes (87). A mean reduction in systolic blood pressure of approximately 2mmHg was identified in our study, which is small compared to larger reductions of between 5 and 25mmHg that have been observed following exercise training in hypertensive populations (130). Although blood pressure reduction following exercise training was small in magnitude, on a population scale such a reduction may have a significant impact with respect to primary disease prevention. It is possible that a larger study would have identified greater reductions in blood pressure or a significant difference between the groups; however, this study was not powered to primarily identify differences in blood pressure following exercise training. Blood pressure during exercise was not recorded and may have been affected to a greater extent by exercise training than resting blood pressure.

4.4.4 *Arterial compliance*

Central augmentation index is a measure that describes the pulse velocity contour using applanation tonometry. It is dependent on the degree by which early-reflected pressure waves alter the pulse wave velocity profile. The amount of early pressure wave reflection is dependent in turn on the stiffness of the vasculature. This variable has been shown to increase from 1.6% to 24.1% between the ages of 10 and 70 years (136) and is associated with an age-related reduction in arterial compliance. Arterial compliance can be measured by combining applanation tonometry and Doppler pulse wave aortic velocity data and has been shown to be approximately 40% greater in athletes compared to age-matched sedentary peers (6, 137). A non-randomised trial

of exercise training in older men reported significant improvements in arterial compliance that were greater than the reduction in systolic blood pressure seen in the same study (137). Although it would be reasonable to expect a reduction in augmentation index in addition to an increase in arterial compliance following exercise training, augmentation index and other applanation tonometry variables were not significantly altered in the intervention compared to the control group in our study despite a comparable increase in exercise capacity to that described in the non-randomised trial quoted above. This lack of change in augmentation index is also surprising when the size of this trial is compared to the trial undertaken by Tanaka et al, which showed a positive result. This discrepancy may have been due to the relative insensitivity of the measurements taken and the fact that, in our study, arterial compliance was not calculated by the Windkessel method described by many authors, but only by central augmentation index alone.

Estimates of systemic vascular resistance were also derived from applanation tonometry data. Although systemic vascular resistance reduced more in the intervention compared to the control group, this was not statistically significant and would suggest that exercise training, or increases in exercise capacity, are not associated with significant changes in arterial compliance. Information regarding arterial compliance during exercise is not available from this study and may have shown a greater response to exercise training than resting measurements.

4.5 Conclusions

Older, normal individuals can improve exercise capacity significantly after six months of exercise training. However, no significant change in resting blood pressure, heart rate or arterial compliance between the groups was identified. This

lack of effect may have been due to a type two error i.e., a study too small to detect a difference between the groups. The exercise stimulus appears to have been sufficient to improve exercise capacity significantly, but may need to be maintained for longer than six months before it can produce a significant measurable effect on the vasculature. Studies reporting the effect of exercise training on cardiovascular function in older people have been non-randomised, used small numbers and have not described blinding methods used during data collection and analysis. In contrast, our study was a randomised, controlled trial, involved moderately large numbers of participants and included women. Therefore, despite its lack of positive results it adds important evidence to the current literature in the field of exercise training in older people.

It is becoming increasingly apparent that the quantity and intensity of exercise required to obtain improved fitness may differ from that needed to impact significantly on cardiovascular function or risk factors (148). It is therefore likely that larger and more prolonged randomised studies would need to be undertaken in order to clarify the effects of exercise training on haemodynamic and arterial function in older people. There is a large body of evidence that supports improving fitness in older populations and the population implications of this type of intervention in the longer term could be very large. However, this study fails to provide conclusive evidence that such increases in fitness are accompanied by significant improvements in arterial function or blood pressure.

4.6 Summary

- The exercise stimulus produced significant increases in exercise capacity.

- No significant change in blood pressure, heart rate or arterial compliance was identified.
- The study may have been too small or too short to result in significant change in this normal population.
- These results add important information to what is currently known about the effects of exercise training in older people because trials similar in design to this one are uncommon.

Table 1 Chapter 4**Baseline haemodynamic and exercise parameters**

	Control	Intervention	p
	Mean (SD)	Mean (SD)	
Number	31	32	
Gender (female : male)	17:14	19:13	0.72
Weight (kg)	72.6 (13.5)	68.4 (9.3)	0.16
Height (cm)	167 (8.4)	165 (9.8)	0.28
Body mass index (kg/m ²)	25.8 (3.8)	25.0 (3.0)	0.38
Resting heart rate (b/min)	64 (10)	69 (9)	0.05
Resting systolic BP (mmHg)	138.7 (15)	140.2 (16)	0.69
Resting diastolic BP (mmHg)	77.4 (6.8)	79.6 (7.8)	0.24
VO₂max (ml/kg/min)	29.9 (6.7)	26.5 (5.4)	0.03
VO₂max (ml/min)	2088 (533)	1777 (468)	0.02
Peak exercise heart rate	160 (13)	161 (15)	0.67
Max workload (METS)	10.1 (2.0)	9.5 (2.2)	0.30
Anaerobic threshold (ml/min)	1768 (642)	1588 (550)	0.23

Table 2 Chapter 4
Exercise capacity by gender

	Control	Intervention	P
	Mean (SD)	Mean (SD)	
Men, VO₂max (ml/kg/min)	31.65 (6.31)	28.86 (5.19)	0.17
Women, VO₂max (ml/kg/min)	28.09 (6.84)	24.38 (4.08)	0.05

Table 3 Chapter 4 Changes in parameters of exercise capacity

	Control Mean (SD)	Intervention Mean (SD)	p	Control End	Intervention End	p
VO₂max (ml/kg/min)	29.87 (6.7)	26.46 (5.4)	0.03	28.77 (7.46)	30.72 (6.53)	0.27
Change in VO₂max (ml/kg/min)	-0.49 (3.7)	4.31 (4.7)	<0.0001			
VO₂max (ml/min)	2088 (533)	1777 (468)	0.02	2088 (594)	2066 (567)	0.69
Change in VO₂max (ml/min)	-21.5 (242)	284 (317)	0.0001			
VO₂max / fat free mass (ml/kg/min)	45.78 (11.5)	42.2 (6.8)	0.19	45.4 (8.9)	47.56 (6.2)	0.3
Change in VO₂max / fat free mass (ml/kg/min)	0.2 (8.6)	5.27 (6.8)	0.02			
Time to 90% max predicted heart rate (min)	5.56 (2.52)	4.83 (1.73)	0.16	5.8 (1.72)	4.9 (1.59)	0.05
Change in time to 90% max predicted heart rate	0.27 (1.7)	0.23 (1.9)	0.9			
Maximum workload (METS)	10.06 (2.03)	9.51 (2.16)	0.30	10.13 (2.15)	10.48 (2.23)	0.53
Change in maximum workload (METS)	0.07 (1.22)	0.98 (1.58)	0.01			
Anaerobic threshold (ml/min)	1758 (642)	1587 (550)	0.23	1759 (666)	1790 (622)	0.85
Change in anaerobic threshold (ml/min)	-9.13 (379)	219 (402)	0.02			

Table 4 Chapter 4**Changes in haemodynamic parameters**

	Control	Intervention	p
	Mean (SD)	Mean (SD)	
Resting heart rate (b/min)	64 (10)	69 (8.5)	0.05
Resting heart rate end (b/min)	64 (9)	66 (9)	0.38
Change in resting heart rate (b/min)	-0.4 (7.5)	-3.0 (8.2)	0.19
Peak exercise heart rate (b/min)	160 (13)	161 (15)	0.67
Peak exercise heart rate end (b/min)	155 (13)	161 (14)	0.11
Change in peak heart rate (b/min)	-4.48 (11)	0.03 (8)	0.06
PR interval (ms)	170 (23)	161 (23)	0.15
PR interval end (ms)	167 (22)	168 (19)	0.71
Change in PR interval (ms)	-3.48 (10)	6.88 (23)	0.02*
Resting systolic BP (mmHg)	139 (15)	140 (16)	0.69
Resting systolic BP end (mmHg)	133 (16)	133 (13)	0.97
Change in systolic BP (mmHg)	-5.5 (14)	-7.2 (12)	0.62
Resting diastolic BP (mmHg)	77.4 (6.8)	79.6 (7.8)	0.24
Diastolic BP end (mmHg)	77.4 (6.8)	76.8 (7.2)	0.72
Change in diastolic BP (mmHg)	0.03 (7.6)	-2.79 (7.6)	0.14

*** = p < 0.05**

Table 5 Chapter 4
Changes in applanation tonometry variables

	Control	Intervention	p	Control	Intervention	p
	Mean (SD)	Mean (SD)		End	End	
End systolic pressure (mmHg)	116 (12)	118 (15)	0.52	113 (11)	111 (14)	0.65
Change in end systolic pressure (mmHg)	-2.5 (12)	- 6.1 (12)	0.25			
Pulse height (mmHg)	49 (13)	49 (15)	0.98	46 (14)	46 (11)	0.92
Change in pulse height (mmHg)	-2.4 (3)	-3.2 (11)	0.81			
Systemic vascular resistance	169 (31)	158 (31)	0.19	169 (30)	154 (30)	0.05
Change in systemic vascular resistance	1.59 (18)	-4 (28)	0.37			
Augmentation (mmHg)	14.5 (6.8)	15.1 (7.8)	0.75	13.7 (8)	13.7 (7)	0.98
Change in augmentation (mmHg)	-0.59 (7.3)	-1.5 (6.1)	0.61			
Maximum dP/dt (mmHg/sec)	780 (212)	752 (233)	0.64	734 (263)	719 (139)	0.79
Change in max dP/dt (mmHg/sec)	-36 (186)	-36 (175)	1.0			
Change in central augmentation index (%)	-1.1 (13)	-0.8 (8.1)	0.93			

Chapter 5

Exercise Training Does Not Result in Significant Changes in Diastolic Function in Older People

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Exercise Training Does Not Result in Significant Changes in Diastolic Function in Older People

5.1 Introduction

Increasing age is associated with significant changes in diastolic function (28). A slowing of myocardial relaxation and a reduction in early left ventricular filling have been identified in older people using invasive measurements of left ventricular pressure decay during diastole as well as other techniques such as cardiac magnetic resonance imaging (20). Doppler transmitral flow velocities during early diastole reduce by 50% between the ages of 30 and 70 years (29) and myocardial velocities measured using tissue Doppler imaging of the mitral annulus during diastole (149) also fall progressively with increasing age (32). Several important links have been made between exercise capacity and diastolic function (51, 73), which suggest that the reduction in exercise capacity identified with increasing age may in part be due to changes in diastolic function in older people. Although master athletes are thought to have improved diastolic function compared with sedentary peers (78, 83, 119), the effects of exercise training on diastolic function in sedentary older people are controversial (70, 90, 150). Whilst small, non-randomised studies show improved diastolic function following exercise training (70, 71), these results are not universal (90). Any assessment of changes in diastolic function following training must be made using methods that are not influenced by training induced reductions in heart rate or blood pressure (115). This is now possible using tissue Doppler imaging, which, unlike conventional echocardiographic measurements of diastolic function, is affected to a lesser degree by haemodynamic modifications. Using tissue Doppler imaging to assess changes in diastolic function, a randomised trial was therefore

proposed, to see whether exercise training in older people can alter the changes in diastolic function that are associated with advancing age.

5.2 Methods

These have been described in detail in Chapter 3. In brief, male and female volunteers aged 60 to 80 years were invited to participate in a research program, with the possibility of taking part in six months of exercise training. Each participant underwent screening tests to exclude undisclosed cardiovascular disease. Participants who completed the screening tests without abnormality were then randomised to either six months of exercise training, (the intervention group), or were asked to maintain their pre-trial levels of exercise, (the control group). Diastolic function was assessed at baseline and after six months by echocardiography. Pulsed Doppler transmitral and pulmonary vein flow and tissue Doppler myocardial annular velocities were measured in early and late diastole. A comparison of parameter change in the intervention compared to the control group was performed on an intention to treat basis.

5.3 Results

5.3.1 *Baseline echocardiographic parameters*

Measurements of diastolic function for the entire study population did not show the expected reductions in E velocity and prolongation of IVRT previously described as being present in the majority of people over the age of 65 years (29, 151, 152), (Table 1, Chapter 5). After combining transmitral flow velocity measurements with those obtained following the Valsalva manoeuvre, 70% of all subjects had Grade 1 diastolic function, (abnormal relaxation pattern) and 30% had grade 0 diastolic function, (normal diastolic filling pattern) at baseline. Neither mean left atrial

diameter nor mean left atrial area showed evidence of left atrial enlargement, (Table 1, Chapter 5). Tissue Doppler imaging measurements for the whole group are shown in Table 2, Chapter 5. These confirm a reduction in diastolic mitral annular velocities in early and late diastole that are consistent with age-matched published values, (Table 5, Chapter 5). Baseline echocardiographic variables were not significantly different between the intervention and the control groups, (Table 1, Chapter 5).

5.3.2 *Changes in exercise capacity*

Exercise training resulted in a significant increase in exercise capacity in the intervention compared to the control group, (Table 3, Chapter 4).

5.3.3 *Changes in diastolic function*

Although there was a trend towards a lowering of resting heart rate and blood pressure in the intervention compared to the control group following exercise training, changes in transmitral flow velocities between the two groups were not significantly different, (Table 3, Chapter 5). Changes in IVRT or left atrial area between the two groups were also not significantly different, (Table 3, Chapter 5) and no significant differences in the changes in pulmonary vein flow velocities were identified between the two groups, (Table 4, Chapter 5). Changes in tissue Doppler imaging parameters measured from the septal aspect of the mitral annulus were also not significantly different when comparing the two groups, (Table 3, Chapter 5) and (Figure 1, Chapter 5). There was a small reduction in A' measured from the lateral aspect of the mitral annulus in the control group, -0.13 cm/s, compared to a small increase in A' measured from the lateral aspect of the mitral annulus, +0.94 cm/s, in the intervention group. The difference between the change in A' between the two groups approached statistical significance, $p = 0.05$. The change in E/E' over the

study period was not significantly different when comparing the two groups, (Figure 2, Chapter 5).

5.4 Discussion

This study showed no significant change in left ventricular diastolic function measured using transmitral, pulmonary vein flow or mitral annular velocities despite a significant improvement in exercise capacity following exercise training when comparing the intervention and control groups. A significant effect on cardiovascular function secondary to exercise training has not been confirmed in our study, which was both large in terms of the number of participants, was a randomised controlled trial and measurements of diastolic function were analysed in a blinded fashion using methods that are relatively insensitive to changes in heart rate or blood pressure. These factors make the results of this study robust compared to other studies that have been small, non-randomised or lacked a control group or used traditional echocardiographic measures of diastolic function.

The trend towards increased lateral late diastolic annular velocity as a result of exercise training was unexpected. Other studies that have examined the effects of exercise training on diastolic function have reported improvements in early rather than late diastolic function. Levy et al describes major improvements in early diastolic filling at rest as well as during exercise following exercise training in older people (70). Other small, non-randomised studies that have examined the effect of exercise on diastolic function have reported increased early and decreased late diastolic flow following exercise training (72, 153). However, in these studies diastolic function was measured using methods that are sensitive to changes in heart rate and blood pressure (24, 115), so that observed changes in diastolic function may

have simply been secondary to training induced bradycardia or reductions in resting blood pressure secondary to exercise training (70, 73). Increased mitral annular velocities during early diastole are seen in athletes compared to sedentary adults (85, 154), but myocardial velocities during late diastole have not previously been shown to be significantly different between athletes and sedentary peers. Based on current literature, exercise training would be expected to improve early diastolic function whilst late diastolic function and late myocardial velocities should change little.

5.4.1 *Adequacy of exercise intervention*

The 16% increase in VO_2max seen in our study is similar to improvements in exercise capacity, ranging between 12 and 27% that have been reported in smaller non-randomised studies of exercise training in older people (70, 86, 89). These studies have all identified significant cardiovascular adaptations following exercise training, (Table 4, Chapter 3). Thus, the lack of effect on diastolic function in our study is unlikely to have been due to an inadequate exercise training protocol (70). Perhaps the six-month exercise-training program was too short to change diastolic function? In general, exercise-training programs that last longer than 26 weeks, at an intensity of at least three hours per week at 80% of maximal heart rate, generate the greatest increase in VO_2max in older people (155). However, in these more prolonged studies, most of the increase in VO_2max is seen to occur during the first six months of exercise training. A small, non-randomised study that examined the effects of exercise training on diastolic function recruited participants into a 12 month exercise-training program, which resulted in a 27% improvement in exercise capacity (90). Despite the longer training period and larger improvements in exercise capacity, this study was also not able to identify any significant change in diastolic function following exercise training. In contrast, a five day exercise training program

involving ten participants who achieved substantial increases in VO_2max was able to show significant changes in diastolic function as a result of training (153).

Studies in athletes have suggested that changes in myocardial structure and function, such as regression of physiological left ventricular hypertrophy tend to occur over a much longer period of time than changes in exercise capacity (156). It is therefore likely that, despite a significant improvement in VO_2max , the exercise stimulus in our study was too short to affect a significant change in diastolic function.

5.4.2 *Athletes*

Whilst young athletes may have improved early diastolic filling compared to sedentary peers, this is less apparent when master athletes and their sedentary peers are compared. Peak Doppler transmitral flow velocities and E/A ratios have been shown to be significantly lower and E wave deceleration times slower in older athletes compared to young athletes but no significant association with age has been identified (157). After investigating master athletes and sedentary controls, Jungblut et al concluded that high-intensity endurance training promotes exceptional exercise capacity and stamina but does not appear to alter normative aging effects on left ventricular diastolic function (150).

Diastolic function during exercise

Although some authors have identified improved diastolic function in athletes (119, 147), resting Doppler parameters of left ventricular filling are frequently not different between endurance athletes and sedentary age-matched subjects (73, 81). Nixon et al showed that, whilst resting transmitral filling velocities were not different, during exercise a significant enhancement in Doppler transmitral E velocity and a reduction

in Doppler transmitral A velocity was seen in athletes compared to sedentary peers (80). Matsuda et al measured left ventricular diastolic function during exercise using M-mode echocardiography and compared young athletes with sedentary men of similar age. They described an augmentation of early left ventricular diastolic filling during exercise that was more significant in athletes than controls (158). It is therefore possible that improvements in diastolic function following exercise training were missed in our study, because measurements were taken at rest rather than during exercise.

Tissue Doppler imaging in athletes

One large, observational study identified significantly higher myocardial velocities measured at rest in the posterior wall of the left ventricle in master athletes compared to sedentary peers (119). Another study measured myocardial diastolic velocities in the basal septum of the left ventricle but failed to identify a significant difference between young athletes and sedentary men (154). However, this study did report a significantly higher E' in the inferior wall of the left ventricle in athletes compared to sedentary controls and showed that this measurement correlated with left ventricular end diastolic volume. They concluded that a large left ventricular end diastolic volume may induce earlier and better early diastolic stretching of myocardial fibres, i.e. larger E'. This in turn may induce enhanced systolic performance during effort through a better use of the Frank-Starling mechanism (154). Our study measured tissue Doppler imaging parameters from the mitral annulus rather than the posterior or inferior walls of the left ventricle. This was to minimise the incidence angle between the Doppler beam and myocardial motion, but may have resulted in us missing training related changes that could have been observed in areas of the left ventricle other than those interrogated in this study.

Diastolic function and left ventricular hypertrophy

In patients with pathological left ventricular hypertrophy, altered left ventricular filling velocities are identified (159). However, despite the presence of physiological left ventricular hypertrophy, diastolic function is preserved or even supernormal in athletes. This lack of change in left ventricular diastolic function is confirmed when it is assessed using tagged MRI (99). In athletes, heart torsion and untwisting remain unchanged unlike patients with pathological left ventricular hypertrophy in whom torsion is increased and diastolic apical untwisting is prolonged (99). Thus, an increase in left ventricular wall thickness or left ventricular mass secondary to exercise training should not have any effect on changes in left ventricular filling or diastolic function that may result from exercise training in previously sedentary people.

5.4.3 *Gender differences following exercise training*

Although exercise capacity improves following exercise training to the same relative extent in men and women (76, 146), recent evidence suggests that gender plays an important role in the physiological adaptations to endurance exercise training in older men and women (62, 86, 94). Women are thought to increase exercise capacity by improving peripheral oxygen extraction with no significant increase in cardiac output, whilst men increase exercise capacity by increasing stroke volume with little change in skeletal muscle function (62). However, some studies of exercise training involving postmenopausal women have identified similar magnitudes of arteriovenous oxygen difference following training as men (76), or have shown an increase in resting echocardiographic left ventricular dimensions in response to training (89). In order to address the issue of whether significant gender differences

exist in the physiological responses to exercise training, our data were analysed separately for men and women. Although specific measurements of arteriovenous oxygen difference were not performed, no significant difference was seen in the changes in any measurement of diastolic function or echocardiographic measurement of cardiac size between male and female participants.

5.4.4 *Animal studies*

The results of this trial contradict evidence that has accumulated recently from animal studies regarding the effect of exercise training on diastolic function. The expression of the SERCA2a gene was shown to be lower in old compared to young rats (16). This gene encodes for the calcium ATPase protein that transports calcium in the sarcoplasmic reticulum. Exercise training in rats has been shown to cause an increased expression of the SERCA2a gene (17, 160), resulting in increased calcium reuptake by the sarcoplasmic reticulum (15) and thus improved myocardial relaxation. Improvements in SERCA2a gene expression and activity are thought to be the molecular basis for an attenuation of the age-associated diastolic dysfunction found in senescent rats following exercise training (36). Although other parameters of myocardial function such as passive left ventricular stiffness have been shown to be unaffected by training (160), in animal studies, exercise training has been shown to cause a reversal of some of the molecular changes that result in diastolic dysfunction with advancing age.

5.4.5 *Exercise training and diastolic function in cardiac disease*

The finding that exercise training improves resting diastolic function is less controversial in patients with cardiac diseases than in normal individuals (74, 96). A study examining the relationship between exercise capacity and diastolic function in

patients with dilated cardiomyopathy showed that the greatest increase in VO_2max and the greatest concomitant change in diastolic filling parameters following exercise training occurred in the group of patients who began the study with prolonged early diastolic filling and an E/A ratio that was less than 0.7 (96). Our study was performed in older people who commonly exhibit such transmitral filling patterns. However, although the majority of our study population had grade 1 diastolic function, or abnormal relaxation, the intervention group had an initial mean E/A ratio of 0.90 which is higher than that seen in the group that benefited most from exercise training in the study described above. Other parameters of diastolic function were also relatively normal, (Table 1, Chapter 5) and so the cohort beginning the exercise training did not have significantly abnormal diastolic function as has been described in the majority of people over the age of 65 years (29). Volunteers for aging research that incorporates exercise as a treatment option are likely to be more active than the average elderly individual (63). It is therefore possible that diastolic function was “younger” in our participants than in a more sedentary cohort and therefore less likely to change following an intervention. Baseline measures of diastolic function did not show the expected age-related prolongation in IVRT or reduction in E/A ratio that has been reported to occur in the majority of older adults. Diastolic abnormalities defined by the European Study Group on Diastolic Heart Failure as an E/A ratio of less than 0.5 and an IVRT of greater than 105ms in this age group were present in none of our study participants at baseline (161). This is in agreement with recent data that suggests that the prevalence of diastolic abnormalities in older adults is much lower than had previously been reported (29). 15.8% of adults over 65 years of age in a large population based study were found to have diastolic abnormalities, but this fell to 4.3% when subjects with hypertension, diabetes or coronary artery disease were excluded (161). Our study may have shown positive results if we had

focused solely on trial participants who had significantly abnormal diastolic function at the start of the trial, or if we had recruited patients with hypertension or diabetes instead of concentrating on normal individuals. The decrease in E/A ratio as well as the prolongation of IVRT with advancing age is however a real phenomenon, the nature of which is unknown and although our participants did not have values that would qualify for diastolic dysfunction as defined above, their diastolic function was still significantly different from that seen in young normal adults (20). In addition, the Doppler filling velocities of subjects in our study were similar to those described in the participants of a smaller trial that was able to show an improvement in diastolic function following exercise training in normal older people (153).

5.4.6 *Tissue Doppler imaging parameters and diastolic function*

Values for E' measured at the septal aspect of the mitral annulus were consistent with published values for normal age-matched individuals (32, 118, 162), (Table 5, Chapter 5). E/E' is thought to be the most accurate measure of diastolic function compared to transmitral, pulmonary vein and mitral annular velocities (122). It combines the influences of transmitral driving pressure and myocardial relaxation (122), correlates well with pulmonary capillary wedge pressure, $r = 0.87$, (118) and has been shown to be a legitimate flow-derived index of diastolic function because it is a derivative of the constant volume pump attribute of the heart (163). Unlike transmitral flow velocities (164, 165) tissue Doppler imaging parameters are not affected by physiological hypertrophy secondary to exercise training (85). In our study, E/E' values confirmed a normal cohort with respect to mean left ventricular diastolic pressure, but these values did not change significantly following exercise training.

5.4.7 *Exercise capacity and diastolic function*

Several important links between diastolic function and exercise capacity have previously been documented. During exercise, diastolic filling needs to be augmented significantly and this is achieved by a significant increase in myocardial relaxation, identified by a 25 to 40% reduction in the time constant of relaxation (73). Studies in patients with coronary artery disease have shown a correlation between measures of myocardial relaxation and VO_2max (74). In patients with cardiomyopathy and in normal individuals, a close correlation between VO_2max and the deceleration time of the E wave and the E/A ratio (166, 167) has been documented (70). E/A ratio was also found to be the most powerful predictor of VO_2max in a stepwise multiple regression analysis of data from a group of normal sedentary people and athletes across a large age range (51). In our study, the only diastolic variable to be positively correlated with VO_2max was E/A, $p = 0.0035$ in a univariate analysis, (Graph 1, Chapter 5). However, in the multiple regression analysis, lean body mass was the most significant independent predictor of VO_2max , explaining 54% of the variance, $p < 0.0001$ and diastolic function variables did not significantly predict VO_2max . This may simply reflect the homogeneity of the trial participants with respect to diastolic function and exercise capacity rather than suggesting a lack of correlation between exercise capacity and diastolic function, (Graphs 1 and 2, Chapter 5).

5.4.8 *Role of peripheral oxygen consumption*

Perhaps, as many authors suggest, exercise training has little effect on central cardiovascular function but simply causes an improvement in peripheral skeletal muscle function, peripheral oxygen consumption and increased muscle mass (76)? Studies examining the changes in central haemodynamic parameters following

exercise training have been small and non-randomised and show conflicting results (62, 86). It has been proposed that most of the reduction in exercise capacity that occurs with increasing age can be eliminated if VO_2max is expressed relative to muscle mass, that is, the reduction in VO_2max in older people is due to a reduction in muscle mass with increasing age (53) rather than a change in diastolic or central cardiovascular function. Resistance training has been shown to increase muscle strength in older people but this occurs in the absence of an increase in exercise capacity (87). In addition, changes in exercise capacity were dissociated from changes in body composition in a different exercise training study that identified significant alterations in cardiovascular function following exercise training (86). Other studies have shown improvements in exercise capacities that are achieved through the combined effect of increased cardiac output and a widening of the arteriovenous oxygen difference (168, 169).

Our study did not directly assess peripheral muscle function, however creatinine concentrations were taken before and after training in all participants as well as in the control group. A higher creatinine concentration suggests a larger muscle mass in people with normal renal function (53). There was no significant difference in the change in creatinine concentration in the control compared to the intervention group 0.01 ± 0.006 vs. 0.002 ± 0.009 mmol/l, $p = 0.59$. DEXA scanning was also used in our study to assess total muscle mass or fat free mass in each of the participants at baseline and six months. No significant increase in fat free mass in the intervention compared to the control group following exercise training was identified.

Exercise training results in a number of central and peripheral changes that are inter-related, follow different time courses and have a complex interaction. In addition,

diastolic function is affected by several interdependent haemodynamic and structural variables. Thus, the response of such a system to exercise training is likely to be complex and to vary between individuals. It is likely that both peripheral and central cardiovascular adaptations occur as a response to exercise training, but these changes were too small to be significantly different from the changes occurring by chance in the control group in our study.

5.5 Conclusions

- High intensity endurance exercise training in normal, older people promotes exceptional exercise capacity but does not appear to alter the normative aging effects on left ventricular diastolic function.
- Indices of diastolic function suggested a relatively “young” group at baseline.
- Factors that affect diastolic function may become less modifiable with advancing age.
- Exercise capacity correlated more closely with fat free mass than with indices of diastolic function. This may indicate that peripheral factors play a greater role than diastolic function in the response of older normal people to exercise training.

Table 1 Chapter 5
Baseline diastolic function

	Mean (SD)
Peak E velocity (cm/s)	53.5 (11.7)
Peak A velocity (cm/s)	60.6 (12.6)
E/A ratio	0.91 (0.21)
E deceleration time (ms)	175.2 (37.3)
IVRT (ms)	86.4 (14.7)
Left atrial area (cm ²)	18.1 (3.9)
Pulmonary A wave duration (ms)	116.3 (17.5)
Pulmonary D velocity (cm/s)	40.8 (10.3)

Table 2 Chapter 5

Whole group baseline tissue Doppler imaging parameters

TDI parameter	Mean (SD)
Septal E' (cm/s)	6.9 (1.4)
Septal A' (cm/s)	10.1 (1.4)
Septal S (cm/s)	6.7 (1.0)
Lateral E' (cm/s)	9.5 (2.2)
Lateral A' (cm/s)	11.1 (2.0)
Lateral S (cm/s)	8.7 (1.7)

Table 3 Chapter 5
Changes in diastolic function

	Control	Intervention	p	Control	Intervention	p
	Baseline	Baseline		End	End	
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
E velocity (cm/sec)	54.9 (12)	51.9 (12)	0.30	55.7 (13)	55.6 (10)	0.98
A velocity (cm/sec)	62 (14)	60 (11)	0.47	64 (14)	64 (12)	0.86
E/A ratio	0.91 (0.2)	0.90 (0.26)	0.82	0.86 (0.17)	0.89 (0.21)	0.99
Change in E/A	-0.03 (0.2)	-0.01 (0.2)	0.78			
IVRT (ms)	87 (15)	85 (15)		89 (12)	87 (14)	
Change in IVRT (ms)	1.95 (12)	1.64 (15)	0.93			
Left atrial area (cm²)	19.6 (3)	17.3 (4)		20.8 (6)	16.5 (2)	
Change in left atrial area	1.25 (4.5)	-0.96 (3.4)	0.15			
E' (cm/sec)	7.0 (1.3)	6.8 (1.5)	0.63	6.8 (1.2)	6.7 (1.4)	0.29
Change in E' (cm/sec)	-0.13 (1.5)	0.39 (1.5)	0.18			
E/E'	8.0 (1.7)	7.8 (1.7)	0.64	8.3 (2.1)	8.0 (1.8)	0.46
Change in E/E'	0.28 (2.0)	0.11 (1.7)	0.71			

Table 4 Chapter 5

Changes in pulmonary vein flow velocities

	Control	Intervention	p	Control	Intervention	p
	Mean (SD)	Mean (SD)		End	End	
				Mean (SD)	Mean (SD)	
Systolic pulmonary velocity (cm/s)	55 (12)	56 (14)	0.86	54 (9)	54 (11)	0.99
Change in systolic pulmonary velocity (cm/s)	-2.6 (7)	-0.5 (7)	0.49			
Diastolic pulmonary velocity (cm/s)	42 (12)	38 (8)	0.3	46 (8)	41 (7)	0.04
Change in diastolic pulmonary velocity (cm/s)	2.3 (9)	-1.4 (6)	0.27			
Pulmonary a wave reversal duration (ms)	115 (18)	118 (17)	0.52	120 (23)	118 (21)	0.84
Change in pulmonary a wave reversal duration (ms)	3.9 (21)	-2.1 (15)	0.27			

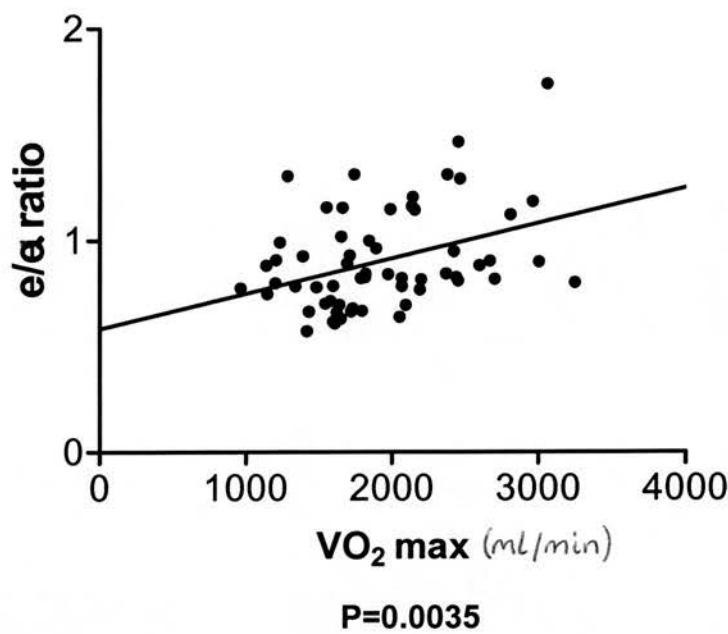
Table 5 Chapter 5

**Reference values for myocardial annular velocities in early diastole in
normal older adults**

Author	E' (cm/sec)	E/E'
Owen (160)	5.5 ± 2.7 73 \pm 2 years	
Sohn (32)	7.5 ± 1.6 60 - 69 years	
Nagueh (116)	12 ± 2.8 59 \pm 10 years	7.7 ± 3
	5.8 ± 1.5 63 \pm 11 years	7.8 ± 3.5
Oxenham (161)	6.88 ± 2.1 60 - 80 years	7.9 ± 1.7

Graph 1 Chapter 5

Correlation between E/A ratio and VO₂max



Graph 2 Chapter 5

Relationship between E/E' and $VO_2\text{max}$ in older normal adults

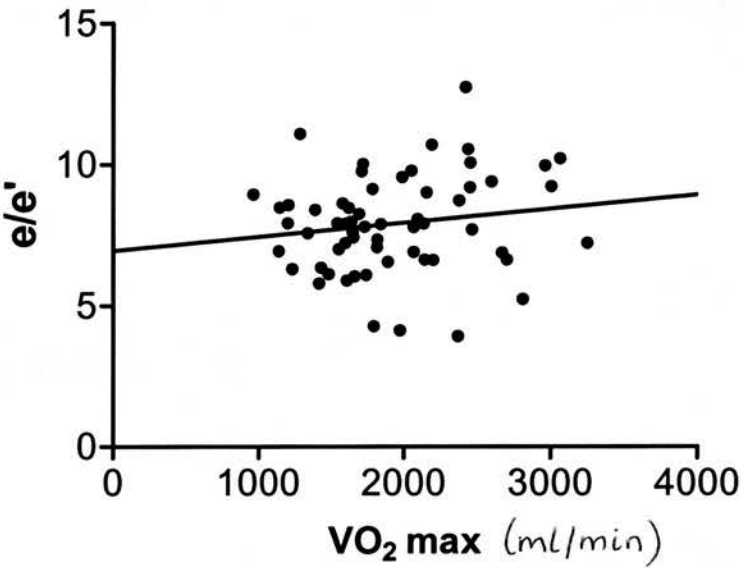


Figure 1 Chapter 5

Changes in E' in response to exercise training

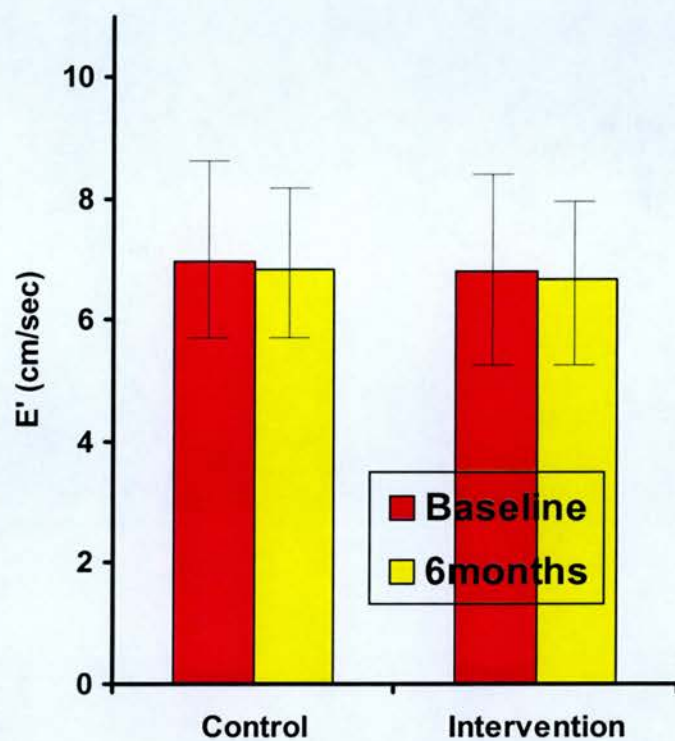
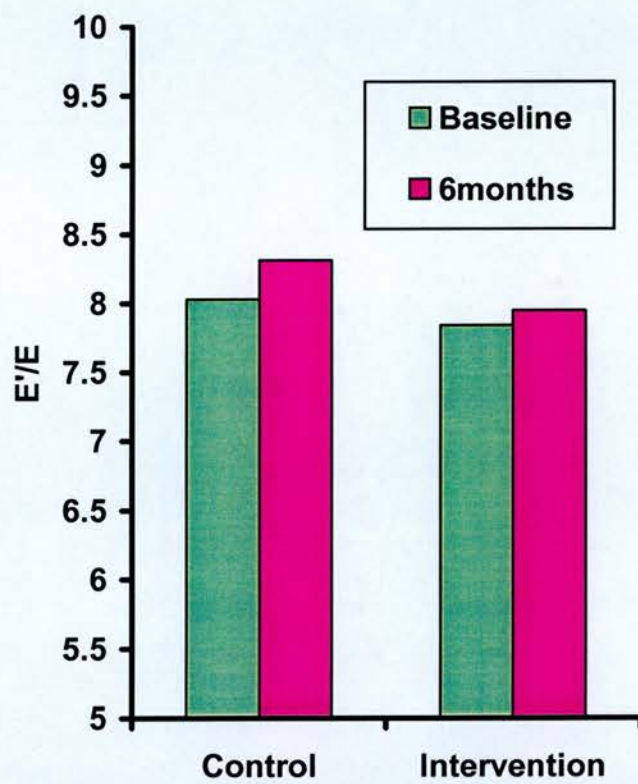


Figure 2 Chapter 5

Changes in E/E' in response to exercise training



Chapter 6

Changes in Lipid Profile and Body Composition Associated with Exercise Training in Older Normal Individuals

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Changes in Lipid Profile and Body Composition Associated with Exercise Training in Older Normal Individuals

6.1 Introduction

Changes in cardiovascular function, increased skeletal muscle mass and improvements in peripheral muscle function following exercise training are thought to result in improvements in exercise capacity in older people. The relative contribution of each of these factors in improving exercise capacity is unclear. Some studies have identified significant changes in central haemodynamic function following endurance exercise training (60), whilst others suggest that increased muscle mass and improved peripheral muscle function is the cause of improved exercise capacity in older people (53).

Changes in body composition and muscle mass as a result of exercise training can be measured in a variety of ways. Traditional methods of estimating body composition such as skin-fold thickness, densitometry and hydrometry are limited in their accuracy, availability and suitability for all populations (131). Dual energy X-ray absorptiometry, (DEXA) is widely used for measuring bone mineral density and can now also be used to estimate whole body composition. It can be performed quickly and easily in older individuals with minimal radiation exposure (132), has a high degree of precision (131) and reproducibility (133) and has been well validated (131). This method was used to estimate changes in body composition in a group of volunteers aged 60 to 80 years who took part in a randomised, controlled trial that compared subjects undergoing a six month exercise training program with a sedentary control group.

Epidemiological evidence suggests a lowering of LDL cholesterol is associated with higher habitual exercise levels (170) and changes in lipid profile have previously been documented following exercise training. However, there are few randomised trials that examine changes in lipid profile following exercise training in people over the age of 65 years, especially in women (170). We therefore assessed changes in lipid profile in this cohort of older adults as well as changes in body composition occurring as a result of exercise training and compared these with changes in a sedentary cohort over the same period.

6.2 Methods

These have been discussed in detail in Chapter 3. Height and body weight were measured to the nearest 0.5cm and 0.1kg respectively at baseline and six months.

Body surface area was calculated using the following equation: -

$$BSA (m^2) = \sqrt{(\text{height (m)} \times \text{weight (kg)} / 36)}$$

Body mass index was calculated by dividing the subjects mass in kg by the square of the height: -

$$BMI (kg/m^2) = \text{weight (kg)} / \text{height (m)}^2$$

Subjects in the control group were specifically requested not to change their usual weekly physical activity during the study period. Levels of weekly activity were assessed at baseline and six months using the physical activity questionnaire (142) as described in Chapter 3. No formal assessment of dietary intake was made during this study, thus information regarding changes in daily caloric intake or dietary composition is not available. All data were analysed using the SAS statistical package on an intention to treat basis and included data from subjects in the intervention group who failed to complete the six month training program. Two-tailed tests were used throughout the analysis.

6.3 Results

6.3.1 Study participants

See Chapter 4, Results.

6.3.2 Lipid lowering drug use

Three of the trial participants were taking lipid-lowering drugs prior to enrolment into the study. The doses of these drugs had remained the same for more than one month prior to randomisation and entry into the study. One man in each group was taking bezafibrate; another man in the intervention group was taking an HMGCoA reductase inhibitor, (Simvastatin).

6.3.3 Hormone replacement therapy

Three of the women in the trial were taking hormone replacement therapy, (HRT) prior to enrolment. This had been started for more than one month prior to the beginning of the trial and no participant stopped or increased their prescribed dose during the trial period. Two of these women were in the intervention and one was in the control group. One other participant began taking HRT during the trial period. This participant was in the intervention group and only completed the first three weeks of the six month exercise training program.

6.3.4 Lipid profile

There was no significant difference in concentrations of cholesterol, triglycerides, LDL cholesterol, HDL cholesterol or cholesterol / HDL cholesterol ratios in the intervention compared to the control groups at baseline, (Table 1, Chapter 6).

6.3.5 *Body composition*

Mean body mass index, (BMI) was $25.4 \pm 3.4 \text{ kg/m}^2$ at baseline for the entire group. Male participants had a mean BMI of $25.33 \pm 3.19 \text{ kg/m}^2$ and a mean body surface area, (BSA) of $1.92 \pm 0.17 \text{ m}^2$ and female participants had a mean BMI of $25.47 \pm 3.61 \text{ kg/m}^2$ and a mean BSA of $1.71 \pm 0.13 \text{ m}^2$ at baseline. Apart from a larger BMI in men in the control versus men in the intervention group, (Table 2, Chapter 6), there were no significant differences in body composition measured by DEXA, between the intervention and control groups at baseline. The women, (n=19) had percentage fat mean values of 41%, (SD 8), while the men, (n=28) had percentage fat values of 26%, (SD 7). These values were higher than expected, however, some of the subjects as well as several members of staff were scanned on the Lunar scanner as well as on a scanner in an adjacent department in order to assess accuracy. Quality assurance measurements for these DEXA % fat estimations showed agreements of between 0 and 1.2% absolute and at most 4% relative to the actual level. These figures are consistent with the between DEXA reproducibility data published in other studies (133).

6.3.6 *Changes in exercise capacity*

Despite a 15.6% dropout rate in the intervention group, there was a significant increase in exercise capacity, $p < 0.0001$, maximal workload and anaerobic threshold in the intervention compared to the control group over the six month study period, (Table 3, Chapter 4).

Physical activity questionnaire scores in the control group did not change significantly over the study period. Activity levels in the control group at baseline were $29.97 \pm 28 \text{ METS}$ and $40.32 \pm 27.1 \text{ METS}$ after six months, $p = 0.16$. The

intervention group increased their activity scores from 28.68 ± 23.8 METS at baseline to 35.21 ± 29.4 METS after six months of exercise training, $p = 0.4$. The difference in the change in activity levels between the control and the intervention groups was not significant, 9.42 ± 29.3 vs. 11.5 ± 27.9 METS, $p = 0.8$.

6.3.7 *Changes in lipid profile*

Triglycerides

There was a statistically significant reduction in triglyceride concentration in the intervention compared to an increase in triglyceride concentration in the control group over the six month period, -0.27 ± 0.36 mmol/l vs. 0.16 ± 0.46 mmol/l, $p = 0.0001$, (Table 1, Chapter 6).

Total cholesterol

No significant change in total cholesterol concentration was identified in the intervention compared to the control group, (Table 1, Chapter 6).

HDL cholesterol

There was a trend towards a greater increase in HDL concentration in the intervention group compared to that seen in the control group. The difference between the change in HDL cholesterol concentration in each group did not reach statistical significance, (Table 1, Chapter 6). There was an increase in HDL cholesterol concentration in the intervention group when comparing baseline with end of study values but this within group change also failed to reach statistical significance, 1.46 ± 0.3 mmol/l, vs. 1.55 ± 0.4 mmol/l, $p = 0.33$.

Cholesterol / HDL cholesterol ratio

There was a reduction in the cholesterol / HDL cholesterol ratio in both groups over the trial period. The cholesterol / HDL cholesterol ratio reduced more in the intervention compared to the control group but this reduction was not significantly greater than that seen in the control group, (Table 1, Chapter 6).

LDL cholesterol

No significant change in LDL cholesterol concentration was identified in the intervention compared to the control group over the study period, (Table 1, Chapter 6).

6.3.8 *Changes in body composition*

BMI and BSA

There were no significant changes in BMI or BSA in either group over the study period, (Table 3, Chapter 6).

Weight

The mean weight loss, measured conventionally as well as by DEXA, was less than one kilogram over the trial period in both groups, (Table 3, Chapter 6). The intervention group lost 0.5 ± 1.75 kg and the control group lost 0.2 ± 2.4 kg. The difference in weight lost between the groups was not significant, $p = 0.67$.

Total body fat

There was a trend towards a greater reduction in total body fat in the intervention compared to the control group but the difference between the groups did not reach

statistical significance. The intervention group lost 1.4 ± 1.65 kg compared to 0.5 ± 2.9 kg in the control group, $p = 0.27$.

Fat free mass

Both groups showed a slight increase in fat free mass. Although the mean increase in fat free mass in the control group was slightly larger than that seen in the intervention group, the difference in the change in fat free mass in the intervention compared to the control group was not statistically significant, (Table 3, Chapter 6).

Total body bone density

There was a small reduction in total body bone mineral density in the control compared to a small increase in bone mineral density in the intervention group, but the difference between the groups was not significant, -0.002 ± 0.01 g/cm² vs. 0.001 ± 0.01 g/cm², $p = 0.48$.

Percentage fat

There was a small increase in percentage fat in the control group over the trial period; initial mean percentage fat was 46.7% at baseline and 47.6% at the end of the study. The intervention group showed no change in mean percentage fat over the six month exercise training period, 48.7% at the start and 48.7% at the end. The difference in the changes in percentage fat between the groups was not significant.

6.4 Discussion

This randomised, controlled study has shown that exercise training results in a significant reduction in triglyceride concentrations as well as trends towards an increase in HDL concentration and lower total to HDL cholesterol ratios in older

normal adults, without significant changes in LDL or total cholesterol concentrations. The changes in lipid profile were observed despite a lack of significant change in body weight or composition.

6.4.1 *Lipid profile*

Exercise is one of the non-pharmacological treatment modalities known to influence lipid and lipoprotein levels (130). Favourable alterations in lipid profiles have been reported among healthy as well as diseased, middle-aged populations following endurance exercise training but the literature is less clear regarding the influence of regular physical activity or exercise training on lipids and lipoprotein levels in older adults (91, 130). Epidemiological studies suggest an association between more favourable lipid profiles and increased physical activity in older populations, (170, 171) but these associations are less strong when adjusted for body mass index (130). Cross sectional studies of postmenopausal female runners confirm an increase in HDL cholesterol with every additional kilometre run per week. Whilst this increase does not depend upon hormone replacement therapy use, alcohol consumption or the subjects' smoking status (172), it is related to a reduction in BMI with larger distances run. Shephard et al performed a meta-analysis of 95 studies of exercise training, most of which were non-randomised and concluded that exercise training leads to a mean reduction of 6.3% in total cholesterol, 10.1% in LDL cholesterol and 13.4% in total to HDL cholesterol ratios (173). However, other authors suggest that exercise training has little effect on total cholesterol or LDL cholesterol concentrations (91) and the quantity and intensity of exercise training required to achieve significant changes in lipid profile are unclear.

There have been few studies that have reported the effects of exercise training on triglyceride concentrations in older people (174). A long term exercise training program in older men and women showed significant reductions in HDL cholesterol but not triglyceride concentrations after two years (148). However, other smaller studies have shown reductions in triglyceride levels following exercise training (175). These results are in agreement with significant increases in triglyceride concentrations that were seen in the intervention compared to the control group in our study as well as studies in younger people and epidemiological evidence that report an association between triglyceride reductions and increased physical activity (171). Raised triglyceride concentrations have been associated with increased incidences of cardiovascular disease and diabetes or abnormal glucose tolerance. This study adds weight to others that suggest a method by which cardiovascular disease could be prevented through increasing levels of physical activity (91, 171). On a population scale, the change in triglyceride concentration could therefore have a substantial impact on incidences of cardiovascular disease.

6.4.2 *Duration and intensity of exercise training*

Whilst exercise training may result in improvements in lipid profile, the magnitude of such changes seem to be related to the duration and intensity of exercise training (175). In a large study involving 120 postmenopausal women aged 50 to 65 years, small but significant increases in HDL cholesterol were observed in the second but not in the first year of home-based exercise training (148). Cross sectional studies in women confirm a dose-response relationship between regular exercise and HDL cholesterol levels (176). Another study showed that a ten week exercise training period was able to favourably affect lipid profiles in older people despite the relatively short duration of the intervention (170), but this training regimen was of

high intensity. Thus, both the quantity and intensity of physical activity required to obtain improved fitness may differ from that needed to have a positive impact on cardiovascular risk factors. Significant improvements in VO_2max in the intervention group confirmed an effective exercise training regimen in our study, but these improvements in exercise capacity were not accompanied, over the short term, by a significantly greater change in HDL cholesterol compared to the control group. It is possible that a significant increase in HDL cholesterol may have become apparent if exercise training had been continued for 12 months or longer, or if the exercise training protocol had been of even higher intensity.

6.4.3 *Gender differences*

Previous studies have concluded that men and women participating in identical exercise programs experience significantly different blood lipid profile responses (177). In order to derive beneficial effects from exercise, it is thought that women have to exercise at significantly higher intensities than men (175). Although exercise is generally accepted as a mechanism to increase HDL cholesterol concentrations in men (175), few well controlled studies evaluating exercise training and HDL cholesterol concentrations in women have adequately considered confounding factors such as hormonal status, cigarette smoking, alcohol consumption, changes in body composition and the use of female hormones. Because many such studies are small, involve exercise training that is of short duration and of low intensity and are uncontrolled, previous authors have concluded that there are insufficient data to demonstrate that exercise training has important effects on HDL levels in postmenopausal women (176, 178). This lack of change in lipid concentrations may be due to the more favourable lipid profiles levels seen in women compared to men at the beginning of exercise training. In our study, baseline HDL cholesterol levels

were significantly higher in women compared to men, 1.51 ± 0.28 mmol/l vs. 1.21 ± 0.35 mmol/l, $p = 0.0004$. Studies have shown that individuals with the most abnormal lipid profiles tend to experience the greatest lipid changes following exercise and diet (177). However, when our data were examined separately by gender, the overall trial results were unchanged. Men in the intervention group increased their HDL cholesterol concentrations from 1.19 ± 0.44 mmol/l to 1.41 ± 0.37 mmol/l but this increase was not significant, $p = 0.17$. Women in the intervention group increased their HDL cholesterol levels from 1.53 ± 0.35 to 1.55 ± 0.4 mmol/l but this was also not significant, $p = 0.13$. HDL cholesterol levels in the control group for both men and women changed very little over the same period. Whilst these results do not support short periods of exercise training as a method by which to increase HDL levels, the discovery of trends towards improved lipid profiles suggests that further, controlled trials, lasting longer than six months may identify significant increases in HDL concentrations following exercise training.

6.4.4 *Weight loss and lipid profile change*

Our study did not find any significant change in body mass, weight or fat free mass as a result of exercise training for six months in older people. A meta-analysis examining the effects of exercise training on lipid levels concluded that changes in lipid levels were dependent on changes in body composition secondary to training (173). Where there is no significant change in body weight a significant decrease in total cholesterol and low-density lipoprotein concentration and an increase in HDL cholesterol levels is seen (173). However, where body weight has been shown to increase, low-density lipoprotein and total cholesterol levels are likely to rise and where body weight decreases, greater reductions in total cholesterol and low-density lipoprotein occur (173). These findings are not universal and studies where large

reductions in weight were noted have failed to show significant changes in lipid profile (177). In our trial, body weight did not change substantially and whilst there was a significant reduction in triglyceride concentrations and a trend towards increased HDL cholesterol levels with exercise, there were no significant changes in total cholesterol or LDL cholesterol. Our study is one of very few trials that have examined this issue in a randomised trial in an older, normal population. However, the inconsistencies in trial findings described above highlight both the wide variations in study design, exercise duration and populations studied as well as the considerable variability in weight change that has been noted to occur in response to a given intervention (179).

6.4.5 *Weight loss*

Changes in body mass are thought to correlate positively with initial body mass, initial percentage fat (180) and to genetic influences (179). Our baseline body composition data indicated that the study volunteers comprised relatively non-obese individuals as would be expected when recruiting participants for an exercise based trial. This would make substantial weight losses more difficult to achieve than if the volunteers had been overweight to begin with and may be one of the reasons for a lack of significant change in weight seen as a result of exercise training. Weight loss also seems to depend upon the duration, intensity and frequency of the exercise-training program (179). Several studies have shown losses in total body mass of more than 10 kg following exercise training, without dieting, over periods of less than 20 weeks. Others have reported weight gain after 12 months of training (181). A review of several hundred exercise training studies concluded that average weight loss over six months would amount to 1.6kg, with a reduction of 2.6kg in fat mass, a 2.9% reduction in body fat and a 1.0kg increase in fat free mass (181). However,

most of the studies reviewed lacked control groups and involved small numbers of participants, thus being heavily influenced by individual variability in the responses to the exercise stimulus (179). The Heritage study achieved smaller reductions in weight than those quoted above and this may have been due to a compensatory increase in energy intake or reduction in spontaneous physical activity by the study participants (181). Few studies have attempted to measure energy intake and physical activity because techniques available to do so are imprecise and time consuming. In our study, no restrictions were imposed upon the participants regarding dietary intake. No assessment of diet was made over the trial period and so we cannot comment on any change in energy intake that may have resulted from participation in an exercise-training program. However, the physical activity recall questionnaire was used in our study in order to verify that the control group maintained pre-randomisation levels of exercise. Questionnaire analysis failed to identify any significant change in activity levels over the study period. Whilst providing useful proof that activity levels in the control group did not increase significantly over the trial period, it became apparent during the trial that these questionnaires showed significant individual variability. Some of the participants in the intervention group mistakenly did not include exercise-training sessions in their total weekly physical activity score making these questionnaires relatively insensitive and inaccurate. Exercise training in the absence of significant alterations in dietary intake is not thought to result in substantial changes in body composition and it is now generally agreed that formal exercise training is more likely to prevent weight gain than to induce significant weight loss (181).

6.4.6 *Fat free mass*

Following exercise training a reduction in fat mass may be observed, with a compensatory increase in fat free or skeletal muscle mass. Thus, a change in total mass or total body weight may not become apparent, even though significant changes in body composition have occurred. Animal studies have revealed sex specific responses in body composition change following exercise training, with females conserving body mass in response to exercise training (180). When our data were examined separately by gender there were no differences in the trial results for the entire group.

6.4.8 *Accuracy of DEXA in detecting change*

Our study failed to detect any significant change in body composition following exercise training. The study may have been underpowered and changes in body composition may have been smaller than could be detected using DEXA scanning. Evans et al found that DEXA was no more accurate than measurements of BMI or skin fold thickness in assessing changes in body composition (182). They reported that the standard error for these methods is such that percentage body fat would have to change by more than 3.8% in order to detect a true change in more than 95% of individuals (182). Clasey et al suggest that because of these margins of error, the use of DEXA alone to estimate percentage fat in an older population is unacceptable in a research setting (132). However, although these reports question the accuracy of DEXA in measuring percentage fat in older populations, this method is thought to provide better estimates of small changes in body composition than densitometry (133) and it has been shown to be particularly good at detecting small group changes in lean mass (133). In view of the significant change in exercise capacity seen in the

intervention group, the lack of observed effect on body composition may have been due to the insensitivity of DEXA scanning. This study was powered primarily to detect changes in diastolic function rather than changes in body composition. The involvement of a non-obese group of subjects will also have reduced the chance of this study to detect significant changes in body composition. Alternatively, subjects may simply have increased their energy intake and dietary composition as a result of the increased energy expenditure needed for exercise training and this might have altered the final body composition figures.

6.4.1 *Study relevance*

Despite the aging of populations in most Western societies, few data are available on the response of lipid profile and body composition to exercise training in older, normal people. The negative health effects of both obesity and unfavourable lipid profiles are well recognised and hold significant health disadvantages in older people in whom cardiovascular morbidity and mortality are high. Most of the existing literature regarding exercise training and lipid profiles or body composition comes from small, non-randomised or non-controlled trials. Few of these trials include elderly subjects and older females represent a particularly understudied population (170). It has been clearly shown that older people are capable of increasing exercise capacity significantly following exercise training and that supervised exercise programs are safe in this age group (91). However, the effects of exercise training on lipid profiles are often inconclusive or show discrepancy with other studies due to the wide variations in duration and intensity of exercise that is undertaken in these studies (170). Whilst marked improvements in exercise capacity and obesity indexes, as well as modest improvements in plasma lipids are possible in elderly women with coronary artery disease following cardiac rehabilitation (174), it seems apparent,

from this study, that significant improvements in lipid profiles are also achieved in normal, older adults. These results have important consequences if translated to a population scale and identify a useful treatment that could be directed at individuals with “metabolic syndrome” in whom triglyceride levels are raised. However, there seems to be no ideal exercise prescription for improving blood lipid profiles in normal, older people of both sexes and across exercise and obesity levels (170).

6.5 Conclusions

- Exercise training results in significant improvements in exercise capacity in older people.
- Significant reductions in serum triglyceride concentrations as well as trends towards improvements in lipid profiles are also noted despite a lack of substantial change in body composition.
- Exercise training is therefore useful to achieve favourable changes in lipid profiles in older people but cannot be promoted on its own as a method by which to change body weight or composition.

Table 1 Chapter 6
Changes in lipid profile

	Control Mean (SD)	Intervention Mean (SD)	p	Control End Mean (SD)	Intervention End Mean (SD)	p
Triglycerides (mmol/l)	1.51 (0.6)	1.57 (0.7)	0.73	1.67 (0.79)	1.3 (0.7)	0.05
Δ Triglycerides (mmol/l)	0.16 (0.5)	-0.27 (0.4)	0.0001			
Total cholesterol (mmol/l)	5.65 (0.8)	5.55 (0.8)	0.62	5.51 (0.83)	5.49 (0.78)	0.92
Δ Total cholesterol (mmol/l)	-0.14 (0.5)	-0.06 (0.5)	0.52			
HDL cholesterol (mmol/l)	1.38 (0.3)	1.46 (0.3)	0.35	1.42(0.29)	1.55 (0.37)	0.16
Δ HDL cholesterol (mmol/l)	0.04 (0.15)	0.10 (0.16)	0.33			
Cholesterol/HDL cholesterol ratio	4.29 (1.1)	4.05 (1.0)	0.35	4.05 (1.09)	3.69 (0.92)	0.16
Δ Chol/HDL cholesterol ratio	-0.24 (0.5)	-0.36 (0.4)	0.29			
LDL cholesterol (mmol/l)	3.6 (0.8)	3.4 (0.7)	0.29	3.32 (0.8)	3.34 (0.7)	0.93
Δ LDL cholesterol (mmol/l)	-0.28 (0.5)	-0.06 (0.4)	0.07			

Table 2 Chapter 6
Body composition at baseline

	Control	Intervention	p
	Mean (SD)	Mean (SD)	
Weight (kg)	72.6 (13.5)	68.4(9.3)	0.16
Height (cm)	167(8.4)	165(9.8)	0.28
BSA Males (m²)	1.95 (0.19)	1.88 (0.13)	0.21
BSA Females (m²)	1.73 (0.14)	1.69 (0.13)	0.41
BMI Males (kg/m²)	26.45 (3.4)	23.74 (2.58)	0.03
BMI Females (kg/m²)	25.22 (4.05)	25.69 (3.26)	0.71

Table 3 Chapter 6
Changes in body composition

	Control Mean (SD)	Intervention Mean (SD)	p	Control End Mean (SD)	Intervention End Mean (SD)	p
BSA (m²)	1.83 (0.2)	1.76 (0.16)	0.12	1.82 (0.2)	1.75 (0.16)	0.16
Δ BSA (m²)	-0.01 (0.04)	-0.01 (0.01)	0.79			
BMI (kg/m²)	25.8 (3.8)	25.0 (3.0)	0.38	25.5 (3.8)	24.9 (2.7)	0.47
Δ BMI (kg/m²)	-0.25 (0.9)	-0.09 (0.9)	0.51			
Weight (DEXA)(kg)	72.3 (13)	69.6 (10)	0.4	71 (12)	67.6 (7)	0.32
Δ Weight (DEXA)(kg)	-0.2 (2.4)	-0.5 (1.8)	0.64			
Total body fat (kg)	33.8 (8.9)	33.9 (9.8)	0.98	33.8 (9.1)	32.9 (11)	0.75
Δ total body fat (kg)	0.0001 (2.8)	-0.92 (2.6)	0.2			
Free fat mass (kg)	43.2 (8.5)	42.4 (9.4)	0.72	44.1 (8.9)	42.6 (9.6)	0.55
Δ Free fat mass (kg)	0.89 (5.6)	0.26 (0.8)	0.56			
Fat (g)	24003 (8680)	22752 (7800)	0.58	22726 (9118)	20772 (8270)	0.49
Δ Fat (g)	-524.7 (2901)	-1407 (1650)	0.27			

Chapter 7

Lean Body Mass Rather than Left Ventricular Diastolic Function Predicts Maximal Exercise Capacity in Older Normal Individuals

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Lean Body Mass Rather than Left Ventricular Diastolic Function Predicts Maximal Exercise Capacity in Older Normal Individuals

7.1 Introduction

The most commonly used measure of aerobic capacity is maximum oxygen consumption during exercise, (VO_2max) expressed as millilitres of oxygen per kilogram body weight per minute. Factors that limit maximum exercise capacity in normal subjects remain disputed. Previous studies have suggested that left ventricular diastolic performance contributes significantly (51), whilst skeletal muscle mass has been shown to be an independent predictor in subjects with heart failure (96). We aimed to identify the relative contributions of left ventricular diastolic function, anthropometric variables and resting cardiovascular function to VO_2max , measured in millilitres per minute in a cohort of normal older people.

7.2 Methods

These have been described in detail in Chapter 3.

7.2.1 Subjects

Male and female volunteers between the ages of 60 and 80 years were recruited into the study after responding to newspaper advertisements. Screening tests to exclude significant coexisting disease included a 12 lead ECG, treadmill exercise test, transthoracic echocardiogram and serum glucose estimation.

7.2.2 *Estimation of $VO_2\max$*

Maximal exercise capacity, $VO_2\max$, was quantified one week after the treadmill exercise test in all screened participants. Subjects were fitted with a breathing mask and walked or ran on a treadmill until exhaustion. The speed and inclination of the treadmill were increased at regular intervals. Heart rate was recorded constantly using a heart rate monitor and respiratory gas analysis was performed every 15 seconds using a Schiller CS-100 analyser. Maximal exercise capacity was defined as the attainment of two or more of the following: -

- A plateau in oxygen uptake, (VO_2) despite increasing workload
- The attainment of greater than age-predicted maximum heart rate ($220 - \text{age}$)
- A respiratory exchange ratio greater than 1.1.

Figure 1 Chapter 7
Measuring $VO_2\max$



7.2.3 *Diastolic function*

Resting diastolic function was assessed using transthoracic echocardiography. The following measurements were made: -

- Doppler transmitral flow velocities during early, (E) and late, (A) diastole, measured at the mitral annulus.
- Mitral annular velocities using tissue Doppler imaging during diastole. E' was the peak mitral annular velocity during early diastole and A' was the peak mitral annular velocity during late diastole. These measurements were taken at the septal as well as the lateral aspects of the mitral annulus using an apical four chamber view, adjusting the transducer in order to minimize the angle between the ultrasound beam and the movement of the mitral annulus.

7.2.4 *Body composition*

Lean body mass was measured using total body dual energy X-ray absorptiometry, (DEXA). The scanner produces radiation beams that scan the body in 1cm intervals. When the beams pass through the body, attenuation of the radiation depends upon mass and tissue type. On the basis of regional attenuation, the total fat free mass of the arms and legs were calculated and these values were added to appendicular fat free mass to obtain total body fat free mass. Fat free mass and fat mass were expressed as a percentage of body weight as well as in absolute values.

7.2.5 *Statistical analysis*

A relationship between diastolic, anthropometric variables and VO_2max was assessed using a variety of iterative multiple regression techniques.

7.3 Results

Out of 87 subjects who were screened, 63 subjects were recruited into the study. They had a mean age of 67 years, (range 60-79 years) and 57% were women. Mean body mass index was $25.4 \pm 3.4 \text{ kg/m}^2$ and mean body surface area was $1.8 \pm 0.2 \text{ m}^2$. Mean VO_2max was 1880 ml/min (range 927 to 3063 ml/min).

7.3.1 Univariate analysis

In the univariate analysis the only diastolic variable to be positively correlated with VO_2max was E/A, $p = 0.0035$.

7.3.2 Multivariate analysis

In the multiple regression analysis, lean body, (fat free) mass was the most significant independent predictor of VO_2max , explaining 54% of the variance, $p < 0.0001$. Maximum workload, (METS) accounted for an additional 11% of the variance, $p = 0.0002$, body mass index for 7% of the variance, $p = 0.0004$ and resting heart rate for 4%, $p = 0.0055$, (Graphs 1 and 2, Chapter 7).

7.4 Discussion

These data suggest that lean body mass is a stronger independent predictor of exercise capacity than diastolic function or other anthropomorphic or resting haemodynamic variables in normal, older men and women. VO_2max is a widely used parameter to estimate exercise capacity or fitness. In sport it is used to assess the efficacy of training regimens and is routinely used in the functional assessment of patients with heart failure who may be considered for heart transplantation. Correcting absolute VO_2 for fat free mass rather than body weight may therefore

enhance the value of VO_2max in predicting outcome and in defining functional status.

7.4.1 *Factors that affect VO_2max*

The factors that limit VO_2max in normal subjects remain disputed. The physiological response to exercise involves the peripheral muscles, the cardiovascular and neuroendocrine systems and blood volume. Each is a potential limiting step in this complex adaptation. Two opposing theories are proposed to explain individual variations in exercise capacity in normal adults. One suggests that peripheral factors limit exercise capacity and the other that cardiovascular function limits maximal exercise capacity (51).

Peripheral factors

Because nearly all the oxygen consumed during maximal aerobic activity occurs in the exercising muscles, it is highly plausible that this is where limitation to exercise capacity occurs (53). Rodeheffer et al found no change in peak cardiac output that could account for the reduction in VO_2max seen older humans (64) and concluded that reductions in VO_2max with advancing age are primarily due to peripheral rather than central factors. These may include a failure to alter blood flow distribution to the working skeletal muscles or an inability of the muscles to utilise oxygen (169). Other authors suggest that the loss of skeletal muscle mass, (estimated by a decrease in the daily excretion of urinary creatinine), also noted to occur with aging, could explain a large proportion of the age-associated decline in VO_2max (53). However, Ogawa et al measured VO_2max in young and old men and women and concluded that nearly half of the age-related reduction in VO_2max is explained by a smaller stroke volume and the remainder by a lower maximal heart rate and lower

arteriovenous oxygen difference at peak exercise (54). The same group also showed that skeletal muscle oxidative capacity and capillary density are lower in older compared to younger, sedentary subjects but they are not different in younger and older trained individuals. This supports the theory that peripheral factors are more important than central cardiovascular factors in determining exercise capacity in normal adults.

Patients with type 2 diabetes have reduced exercise capacity compared to age and body mass index matched normal subjects (183). This reduction in $\text{VO}_{2\text{max}}$ was found to be due largely to a reduced peripheral arteriovenous oxygen difference in diabetic subjects (184). In non-cachectic patients with heart failure, skeletal muscle mass has been found to independently predict peak oxygen uptake and ventilatory response during exercise (59). This study was one of few studies that assessed skeletal muscle mass using DEXA scanning which is thought to be more accurate and reproducible than other methods of assessment of fat free mass (133). In addition, other factors that may have predicted exercise capacity such as neurohormonal activation, diastolic function and age were not found to be as strong independent predictors of skeletal muscle mass in this group of patients (59). The study also suggested that differences in exercise capacity between men and women are probably due to differences in body composition and indeed Ogawa et al were able to show that sex differences in exercise capacity in sedentary, normal subjects could be largely removed if $\text{VO}_{2\text{max}}$ was normalised to fat free mass.

Central cardiovascular factors

A reduced $\text{VO}_{2\text{max}}$ has been associated with reductions in maximal cardiac output (48), but some authors have suggest that the reductions in peak cardiac output

previously described were in fact the result of undetected cardiovascular disease in older people (48). However, recent papers have suggested that the most important determinant of VO_2max is diastolic function and that it is the change in diastolic function with advancing age that causes the reduction in exercise capacity seen in older people (51, 73). Exercise capacity has been shown to be significantly related to early, (E) and late, (A) transmitral diastolic peak filling velocities across a wide age-range of normal individuals (51). The most powerful independent predictor of VO_2max was the ratio of early to late transmitral filling velocities during diastole, E/A. Peak E velocity was also found to be a predictor of VO_2max in a similar, smaller study (70). Both papers suggest that the shift with advancing age from early to late diastolic left ventricular filling is an important factor in the reduced exercise capacity seen in the elderly. The correlation between diastolic function and exercise capacity has also been observed in patients with dilated cardiomyopathy and heart failure (166, 167). These studies showed that diastolic function was more closely correlated to exercise capacity than measures of systolic function, but neither study examined the influences of peripheral factors such as muscle mass or oxygen extraction on exercise capacity.

The importance of diastolic function in achieving adequate gas exchange during exercise may be critical, despite normal systolic function (71). During exercise-induced tachycardia, left ventricular filling time decreases dramatically. In order to maintain cardiac output, not only do heart rate and contractility have to increase, but also the rate of left ventricular filling must rise substantially (51). If left ventricular relaxation or left ventricular distensibility are impaired, as is the case in older normal people (5), then left ventricular filling rates may be too low to achieve adequate cardiac output during exercise.

In the studies quoted above, subjects with higher exercise capacities had faster peak early left ventricular filling velocities and higher ratios of early to late filling than those subjects with lower exercise capacities (51, 70). These higher early diastolic filling velocities have also been described in observational reports comparing athletes and untrained individuals (158). In our study we were not able to show that resting diastolic function parameters had a significant impact on exercise capacity. We measured diastolic function using standard as well as newer, more robust measures such as tissue Doppler imaging, but these newer measures of diastolic function were also not significantly correlated to exercise capacity.

Effects of training

Master athletes can have VO_2max values that compare favourably with sedentary young adults; thus, VO_2max must also depend to a certain degree, upon life-style, health status and genetic endowment (48). Exercise training is acknowledged to increase VO_2max substantially in both young and old sedentary individuals (47). These increases in VO_2max may be due to improvements in cardiovascular function or changes in peripheral muscle function or skeletal muscle mass following training. There have been numerous small studies that have attempted to evaluate cardiovascular change following exercise training and a similar number that have concluded that peripheral muscle function change rather than central cardiovascular function is responsible for improvements in VO_2max following training (71, 76). Unfortunately, few studies have measured both central cardiovascular function and peripheral muscle function in response to training in order to evaluate the relative contributions of each.

7.4.2 *Limitations of the study*

Peripheral arteriovenous oxygen difference, which gives an indication of peripheral oxygen use and thus oxidative capacity of the peripheral muscles, was not measured in this study. Older people may have a reduced ability to shunt blood to exercising muscles (28), but this was not assessed in our study. Blood volume change can also affect exercise capacity by increasing oxygen delivery to the tissues but this factor was also not specifically measured (59).

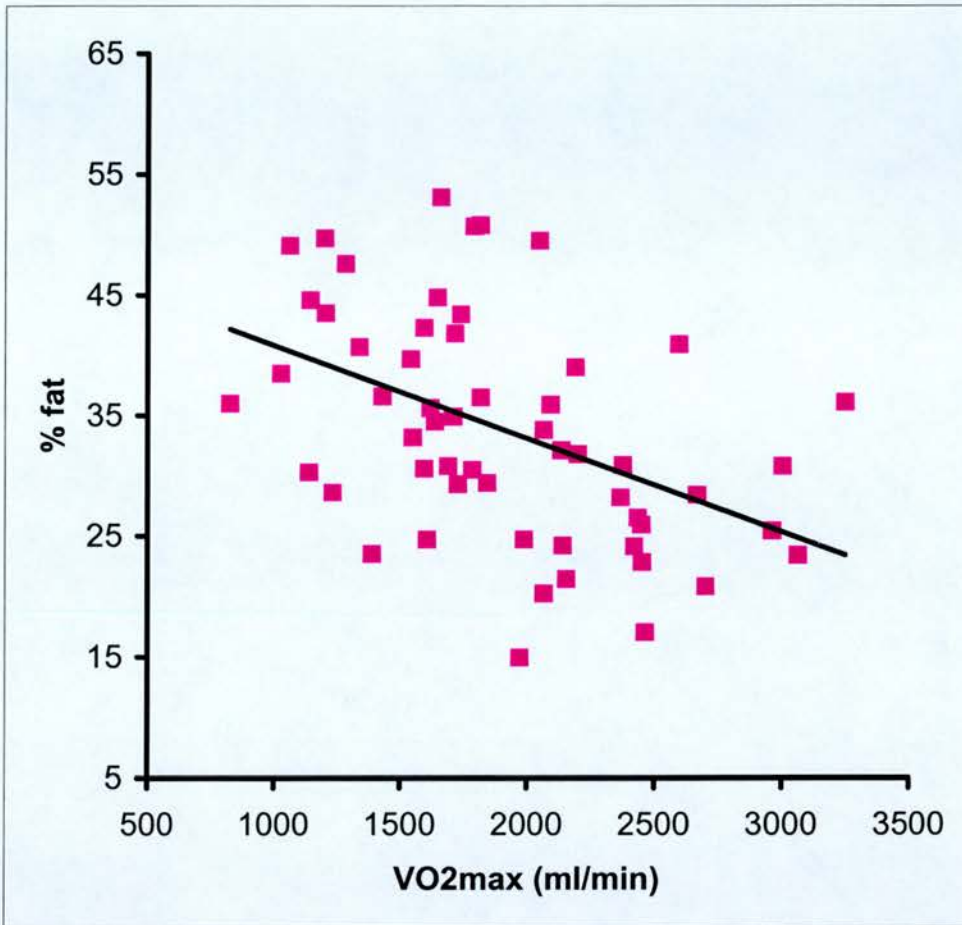
Our study compares resting diastolic and anthropometric variables with parameters of maximal exercise. Although individual variations in diastolic function may change during exercise, other studies suggest that this is not the case (158) so that it would seem reasonable, although not ideal, to compare measures of diastolic function at rest to exercise variables. In addition, supine measurements made during echocardiographic examinations have been compared in this study with exercise parameters measured with subjects in the upright position. However, alterations in transmitral flow velocities associated with posture change have previously been shown to be modest (166).

7.5 *Conclusions*

- In a cohort of healthy, older men and women, fat free mass is the most important independent predictor of exercise capacity.
- Diastolic function was not found to be associated significantly with exercise capacity in a multivariate analysis.
- Normalising measures of exercise capacity to fat free mass rather than body weight could make this measurement of fitness or functional capacity more accurate and relevant.

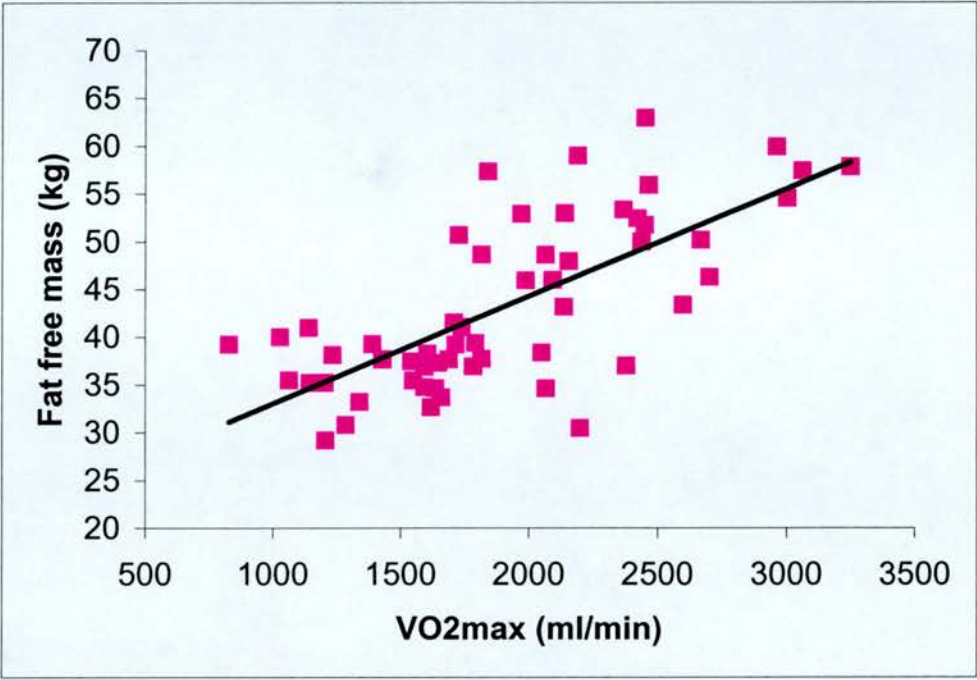
Graph 1 Chapter 7

Correlation of %fat with VO₂max in older normal individuals



Graph 2 Chapter 7

Correlation of fat free mass with VO_2max in older normal adults



Chapter 8

Changes in Cardiac Structure Following Exercise Training in Older Normal Individuals

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Changes in Cardiac Structure Following Exercise

Training in Older Normal Individuals

8.1 Introduction

A considerable number of cross sectional studies have described how long-term athletic training is associated with cardiac morphological changes such as increased left ventricular mass, changes in left ventricular cavity dimensions and increased myocardial wall thickness (185, 186, 187). Left ventricular hypertrophy occurs in approximately 20% of male and 39% of young female, elite athletes (157) and although there have been few studies examining cardiac structure in older athletes, physiological left ventricular hypertrophy in this group is thought to be relatively common (157). Unlike patients with pathological left ventricular hypertrophy, the ratio of left ventricular cavity size to wall thickness remains within normal limits in athletes (154) and resting systolic and diastolic function is normal (188).

Whilst some studies suggest that exercise training causes an increase in left ventricular mass (70), others show ambiguous results (94). Most intervention studies looking at the effect of exercise training on cardiac size have been small, non-randomised and have measured changes in cardiac structure using methods that are relatively insensitive to the small changes that could be expected following brief episodes of exercise training (189). Few studies have been conducted in older people, or have used what is currently considered the gold standard method to evaluate cardiac morphology and function, namely cardiac MRI (109, 190).

We conducted a study in older, normal people to see if significant changes in left ventricular size and mass could be observed in previously sedentary older adults who

had undergone six months of exercise training compared to age-matched individuals who remained sedentary over the same time period.

8.2 Methods

These have been described in detail in Chapter 3. The MRI protocol and analysis has been described in Chapter 2. Calculation of left ventricular mass and volumes were performed using three dimensional data from MRI images. Calculation of left ventricular mass from echocardiographic measurements used the following formula in accordance with the American Society of Echocardiography: -

$$0.8 (1.04(LVEDD/10 + IVS/10 + PW/10)^3 - (LVEDD/10)^3) + 0.6).$$

8.2.1 Power calculation

Previous studies have shown that, using cardiac MRI, nine patients are required to detect a change of 10 grams in left ventricular mass, whilst the number needed using echocardiography to detect the same change is 190. Similarly, in order to detect a change in end diastolic volume of 10 ml, 12 patients are required when using MRI, whilst 97 would be needed with echocardiography (107). Because of funding constraints, as well as the greater sensitivity for detecting change in left ventricular mass compared to echocardiography, only 50% of the study population underwent MRI scanning at the start and the end of the six month study period, whilst echocardiography was performed on all subjects. With 15 subjects in each group who underwent MRI scanning we expected to be able to detect an increase in left ventricular mass of approximately five grams and an increase in left ventricular volume of approximately 10ml. Thus, it was felt that significant changes in left ventricular structure could be identified with these numbers.

8.3 Results

There was a significant increase in exercise capacity in the exercise compared to the control group, (Table 3, Chapter 4). No significant change in heart rate or blood pressure was identified in the intervention compared to the control group over the six month study period, (Table 4, Chapter 4).

8.3.1 MRI data

Left ventricular mass

A significant increase in left ventricular mass was seen in both control as well as intervention subjects, (Table 3, Chapter 8). Although there was a reduction in left ventricular mass in two people, un-indexed left ventricular mass increased by 6.7g (95% CI 3.2-10.3g) in the control group, (n=14) and 8.9g (95% CI 6.3 to 11.5g) in the intervention group, (n=13). These differences were not statistically different from each other, $p=0.33$. In order to eliminate differences between men and women, the measures of left ventricular mass were also indexed to body surface area. Indexed left ventricular masses increased by approximately 4g/m^2 , but indexing to body surface area did not change the overall results, (Table 3, Chapter 8). No associations were identified between the change in left ventricular mass and the change in measures of exercise capacity, (VO_2max) in either group.

Left ventricular dimensions

There was no significant difference between the focal lengths of the ventricles between the two groups at baseline. The end diastolic volume decreased by 4.4ml and the end systolic decreased by 2.6ml on average over all subjects during the trial period. These changes in left ventricular dimension at rest were not significantly different between the control and intervention groups, (Table 3, Chapter 8). Ejection

fraction changed by only 0.9%, (absolute) and this was not significant in either group over the trial period.

8.3.2 *Echo data*

Baseline measurements for the whole group showed normal left ventricular dimensions and left ventricular mass, without evidence of left ventricular hypertrophy, (Table 1, Chapter 8). Unfortunately, only approximately 50% of all echocardiographic studies had images that were adequate to calculate left ventricular mass at both baseline and end of study. In the control group, there was a mean decrease in left ventricular mass of 3.9g, (SEM 5.4g), over the trial period, but this decrease from baseline values was not significant, $p=0.68$, Table 2, Chapter 8. The intervention group showed a mean decrease of 1.4g, (SEM 4.7g), which was also not significantly different compared to baseline for this group, $p=0.78$. The difference between the change in mass in the two groups was also not statistically significant, $p=0.72$. Overall no significant change in left ventricular mass was seen over six months, (mean -2.6 g, 95% CI -9.7 to $+4.5$, $n=46$). In the analysis of those subjects who had both echocardiographic and MRI data, no change in left ventricular mass was seen from echocardiography, (mean 1.6 g, 95% CI -9.0 to $+12.1$ g) but an increase in left ventricular mass of 8.3 g was seen from MRI data, (95% CI 6.2 to 10.3 g).

No significant differences were seen in the changes in left ventricular dimensions between the intervention and the control groups, (Table 4 Chapter 8). There were also no significant differences in the changes in left ventricular wall thickness at either the posterior wall or the interventricular septum between the two groups, (Table 4, Chapter 8).

8.4 Discussion

MRI data from our study identified a substantial increase in left ventricular mass without large changes in left ventricular dimensions in the group that underwent exercise training. Without a control group our results would have been resoundingly positive, suggesting that physiological left ventricular hypertrophy does accompany improvements in exercise capacity in older people. However, the presence of a control group makes this conclusion untenable because increases in left ventricular mass were also seen in this group.

The results of our trial are surprising and suggest relatively large increases in left ventricular mass in both groups when considering the MRI data, without significant change in left ventricular mass measured using echocardiography. Why did both groups show an increase in left ventricular mass measured using MRI over the trial period? Perhaps the control group increased its activity levels over the trial period? The recruitment period took place over a six month period so that changes in normal daily activity levels between summer and winter are unlikely to be the cause of these results. In addition, no significant increase in physical activity was identified from the physical activity questionnaires that were administered at the beginning and end of the study to all the participants. However, subjects in the control group may have secretly increased their exercise levels and were not able to admit this because they had agreed not to at randomisation. Additional evidence for stable activity levels in the control group during the trial comes from the absence of improvements in exercise capacity in the control group between baseline and end of study. Whilst $\text{VO}_{2\text{max}}$ measurements were unblinded, each participant's baseline $\text{VO}_{2\text{max}}$ value was unknown to the technicians that performed the test in order that they were not influenced to stop the test early for control participants. In addition, strict criteria

were applied to define true maximal exercise capacity and so, although measurements of VO_2 max are known to be relatively inaccurate compared to other physiological measurements, it is unlikely that the VO_2 max results were biased towards one group.

There was no significant correlation between changes in VO_2 max and changes in left ventricular mass in the subjects in either group. This suggests that the changes in left ventricular mass could be unrelated to exercise training but it may also suggest inaccuracies in the measurement of VO_2 max in this study. Increases in mass may have resulted from the development of hypertension or coronary artery disease in the trial participants but this is unlikely to have occurred in previously fit, normal adults over such a short time period.

Significant increases in left ventricular mass were not identified using echocardiographic data. Echocardiography is known to be less accurate and less sensitive than cardiac MRI for detecting small changes in left ventricular morphology, however the lack of significant change in cardiac structure was expected, given the lack of significant change in many of the other parameters measured in this study.

The results of our study show no significant change in cardiac structure or mass using echocardiography but a significant increase in left ventricular mass without substantial chamber enlargement in both groups using MRI data. Perhaps, given the incongruous nature of the MRI results with respect to echocardiographic and haemodynamic data, these results are spurious and no significant change in cardiac structure was present? Were there were errors in the way that left ventricular mass

was measured using MRI? Because of the unexpected results from the MRI data, a review was conducted in order to determine whether errors had occurred in this analysis.

8.4.1 *Review of MRI data*

Intra and inter-observer variability

All cases were reviewed to determine consistency in placement of the base plane on the mitral annulus. Some anomalies were corrected, but this resulted in small changes only. A second observer performed an independent analysis of 12 cases, (20% of the total study) chosen at random. This observer was blinded to the subjects' name and whether the scan was at baseline or six months. At no stage during the analysis or review process were any of those involved un-blinded to the control and intervention groups. Only two frames of the magnetic resonance sequence were analysed in the interests of time. Therefore, this comparison may provide data on bias between observers but cannot be used to estimate precision, as mass estimates are more precise when all frames in the sequence are analysed. Despite some scatter, the average difference in mass between observers was 2.9g and there was no significant difference between the results, $p=0.75$. Some differences were found in end systolic volume but these may be due to the fact that the frame chosen for analysis by the second observer may not have been the frame with minimum volume. Some "problem cases" were identified in the dataset in which the long axis slices were not positioned ideally during the acquisition, and/or there were substantial mis-registrations from slice to slice due to variation in breath hold position. Both observers reanalysed these cases and a consensus was reached which resulted in better model estimates but did not alter the direction or size of mass change.

Possibility of problems during scan acquisition

We considered that a problem might have occurred at the scanner between baseline and six month studies, leading to an apparent increase in mass in both groups. However, the scanner is calibrated using the standard Siemens protocol quality control tests and this is documented every morning. If there had been some systematic bias in the acquisition due to image scaling or distortion, then it would be expected that along with an increase in mass, the end diastolic volumes and end systolic volumes would have also increased. In fact, the end diastolic and end systolic volumes decreased over all subjects while the mass increased. Thus, an overall scaling error, (such as an error in field of view) is unlikely. Where images were distorted or incorrect, we would have expected that all of the values would have moved the same way.

Analysis

The increase in mass is due to both the endocardial surface moving inwards and the epicardial surface moving outwards, (the epicardial movement was the more dominant effect, removing the possibility that contouring of the papillary muscles were the main source of the increase in mass). The fact that the increase does not come solely from movement of one surface, (particularly the endocardium, which is the most difficult to define) makes it less likely that the change has been caused by drift over time in the position of one contour.

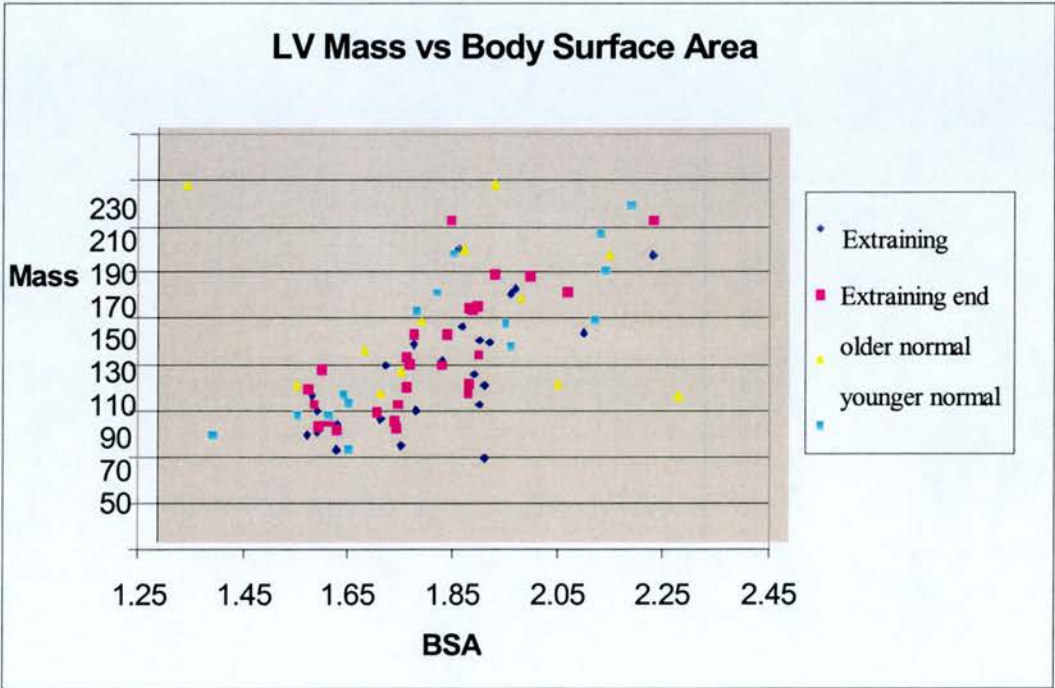
If all the baseline scans had been measured before all the end of trial scans, then it is possible that some learning effect with respect to the measuring technique may have resulted in increases in left ventricular mass in end of study rather than baseline scans. The analysis was performed by the same person on the same computer using

the same version of software and if a learning effect were the cause of this unexpected increase in left ventricular mass in both groups then changes in volume would have also been seen. This was not the case. Existing calibrations against phantoms and other checks have failed to find a measurement error in the software that was used. In any event, any computational errors would be applied to both the control and exercise groups and relate to a comparison to an external gold standard rather than between the two groups.

Comparison with existing data

We have compared the exercise masses to our pre-existing older normal and younger normal databases, (normalised for body surface area) and found no striking differences.

Figure 1 Left ventricular mass versus body surface area



Conclusion

We have not found any obvious error in the analysis. Some problem cases have been reanalysed but this did not change the direction of mass change. The cause of this increase in mass in both groups is therefore unclear but cannot easily be explained by errors in analysis or data acquisition.

8.4.2 *Athletes*

It is generally believed that cardiac enlargement is an adaptive response to exercise training. This concept is in large part, based on the indirect evidence from numerous cross sectional studies that show larger hearts in highly trained athletes compared to sedentary individuals (76). Direct evidence of cardiac enlargement as a result of exercise training in previously sedentary individuals is however sparse, particularly in older populations (189).

Studies of young athletes using MRI have confirmed a significant increase in left ventricular mass (75) and end diastolic volume, with no significant change in left ventricular volume to mass ratio (156) or end systolic volume compared to controls (190). Bouvier et al found no difference in resting left ventricular size in master athletes compared to age-matched sedentary peers (78), whilst Seals et al identified larger stroke volumes among veteran athletes compared to age-matched sedentary controls due to physiological volume overload hypertrophy and improved systolic function (76). In general, whilst many studies have evaluated cardiac structure in young athletes, little is known about cardiac size and shape in athletes over the age of 70 years (78).

8.4.3 *Left ventricular structure change as a response to exercise*

Despite similar training and exercise capacity there is considerable variation among endurance athletes in the development of changes typical of athletic heart (159).

Training induced left ventricular hypertrophy may be influenced by several factors such as gender (157), the type of sport performed and genetic or racial background (187). Dynamic-type endurance athletes tend to develop larger left ventricles without significant left ventricular hypertrophy, whilst resistance training is more likely to result in left ventricular hypertrophy (159). An exercise training study that included young monozygotic twins also identified a significant genetic link regarding the response of cardiac structure to training (191). Genetic variables are thought to be a major determinant of left ventricular mass in children as well as middle-aged adults (192), but D polymorphism of the ACE gene may only be of importance in specific circumstances such as training-associated left ventricular hypertrophy (159).

8.4.4 *Previous studies using exercise training*

The results of cross sectional studies cannot be ascribed directly to exercise training and longitudinal studies in athletes may simply identify a genetic component that has caused structure change. Echocardiographic evaluations of the effect of exercise training on cardiac dimensions in previously sedentary subjects have been less consistent than those evaluating athletes (90). Intervention studies described in the literature have numerous procedural and methodological shortcomings and are difficult to interpret (189). In many training studies the intensity and quality of exercise is not described, nor is adherence or the change in exercise capacity, (VO_2max) that has resulted from the training stimulus. Often, whilst jogging or walking is used during training, cycle ergometers are used when measuring VO_2max (189). Thus, whilst Landry et al conclude that cardiac dimensions are amenable to

significant modification under controlled endurance training conditions (191), other small, non-randomised studies have shown no significant change in left ventricular size or mass following exercise training in previously sedentary young people (193), even when training has continued for twelve months (90).

Intensity

In addition to the inconsistencies described above, other factors may promote controversy regarding the response of cardiac structure to exercise training. Firstly the intensity of training varies between studies and this may be an important factor in the cardiac response to training. Two studies reporting positive findings both achieved increases in VO_2max of approximately 30%, (189, 191), whilst other studies that have failed to report significant left ventricular change have achieved smaller increases in VO_2max of approximately 18% (193). In our study, VO_2max change was 16% absolute and 19% increase relative to the control group. Thus, it is possible that cardiac structure change requires relatively intense or prolonged training with substantial increases in VO_2max .

Age

Age may be another factor that affects the results of training studies. An interaction between age and the effects of training on the heart was suggested from animal experiments that revealed significant cardiac adaptation in juvenile but not in older rats following similar training regimens (193). Shapiro et al concluded that a significant increase in left ventricular wall thickness and mass may develop in untrained young volunteers after a period of moderate intensity exercise (194) and Levy et al identified significant increases in left ventricular mass when men aged less than 32 years underwent six months of exercise training. However, non-significant

increases in left ventricular mass were observed when men aged 60 years and older went through a similar training regimen (70). Thus, the large ventricular volumes exhibited by athletes may be the result of training during a critical period prior to attainment of maturity. Almost all training studies that have examined left ventricular structure change have involved young adults rather than older subjects. A controlled trial in postmenopausal women did identify significant changes in ejection fraction and left ventricular end diastolic diameter compared to baseline values despite an increase in VO_2max of only 12%, however these results were not significant when compared to the control group (89). A similar, small study in men aged 60 to 70 years also showed small cardiac morphological changes in response to training (93), but a randomised controlled study of exercise training in older men using resistance training for 16 weeks was unable to detect significant change in cardiac structure or function as a result of the training stimulus (195). The echocardiographic evidence from our study supports the concept that there may be an age-mediated diminution in the ability of the left ventricle to alter its shape or size as a result of exercise training.

Heart rate

Other investigators have observed that changes in heart rate following exercise training are linearly related to changes in left ventricular volume. Thus, the left ventricular volume change following training that has been reported in some studies may have simply been as a result of training induced bradycardia (116). Because small increases in cardiac dimensions can be magnified by formulas that are used to calculate cardiac mass and volume, the use of echocardiography to measure changes in cardiac structure may identify a change secondary to training induced bradycardia that would not be apparent if left ventricular structure was assessed using cardiac MRI.

8.4.5 MRI

The use of MRI to measure changes in myocardial mass has been demonstrated to have superior precision and reproducibility relative to other imaging techniques (109, 116, 190). This technique is uniquely suited to quantify changes caused by remodelling because it can non-invasively image the entire left ventricle (116). In calculating myocardial mass, epicardial definition is excellent and measurements are independent of geometrical assumptions (188). Thus, MRI has been used as a reference method for accurate assessment of left ventricular mass and volumes (188) because it has superior interobserver variability compared to echocardiography or radionuclide techniques (116). Smaller numbers of subjects are required to detect significant change and this makes MRI an excellent choice when examining left ventricular structure change in relatively small numbers of subjects (107). Echocardiographic studies require 190 subjects in order to have an 80% chance of detecting an increase in left ventricular mass of 10 grams whereas this number is only nine using cardiac MRI (107). From these calculations it can also be seen that most exercise training studies in the literature that have used echocardiography to detect significant change in cardiac structure, have been underpowered.

There have been few studies that have used MRI to identify change in left ventricular mass as a result of exercise training. One randomised controlled trial of exercise training in middle-aged subjects following a first myocardial infarction showed substantial increases in $\text{VO}_{2\text{max}}$ were not associated with significant change in left ventricular mass or left ventricular dimension size (116).

The unusual results using cardiac MRI to measure left ventricular mass change in our study are difficult to explain. Disappointingly, the most likely cause for their incongruous nature compared to the other findings in this study are that technical errors have limited their accuracy or reproducibility. This is particularly surprising given the accepted superiority of this technique in measuring cardiac structure compared to other methods.

8.5 Conclusions

- Using echocardiographic data, left ventricular mass did not increase significantly due to exercise training.
- MRI data revealed incongruous results regarding increases in left ventricular mass that cannot be explained easily. We felt that, on balance these results were unlikely to represent actual changes and should be discounted.
- Left ventricular chamber dimensions did not change significantly in response to exercise training.
- Older people do not show physiological left ventricular hypertrophy as a result of improved exercise capacity.

Table 1 Chapter 8**Baseline echocardiographic parameters**

	Mean (SD)
LVEDD (mm)	49.41 (4.88)
PW (mm)	7.88 (1.53)
IVS (mm)	8.15 (1.79)
LVEDS (mm)	30.3 (4.01)
FS (%)	38.33 (5.36)

Table 2 Chapter 8

Change in left ventricular mass using echocardiography

Left ventricular mass (g)			
	Baseline	End of study	Difference
	Mean (SEM)	Mean (SEM)	Mean (SEM)
Control	149.98 (10.2)	146.66 (10.5)	-3.93 (5.4)
Intervention	131.24 (7.8)	131.52 (6.5)	1.38 (4.7)

Table 3 Chapter 8 Changes in myocardial structure and function using MRI

	Control	Intervention	p	Control End	Intervention End	p
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Ejection Fraction (%)	71.4 (5.5)	71.3 (4.7)	0.9	72.1 (4.7)	72.9 (4.6)	0.7
Δ Ejection Fraction (%)	0.9 (5.9)	1.6 (4.4)	0.75			
Stroke Volume (ml)	79.3 (11)	77.5 (17)	0.7	77 (13)	84 (16)	0.2
Δ Stroke Volume (ml)	-2.7 (11)	0.5 (10)	0.7			
ESV (ml)	33 (12)	34 (9)	0.7	30 (7)	32 (9)	0.5
Δ ESV (ml)	-3.4 (8)	-2.3 (5)	0.7			
EDV (ml)	112 (21)	117 (17)	0.5	107 (17)	116 (23)	0.2
Δ EDV (ml)	-6.1 (12)	-1.8 (11)	0.3			
LV mass (g)	123 (28)	127 (23)	0.7	132 (29)	136 (25)	0.7
Δ LV mass (g)	6.8 (6)	8.9 (4)	0.3			
LV mass/BSA (m²)	62.3 (10)	63.2 (11)	0.7	67.8 (10)	68 (11)	0.7
Δ LV mass/BSA (m²)	2.2 (3.6)	3.2 (2.7)	0.6			

Table 4 Chapter 8

Changes in left ventricular structure using echocardiography

	Control	Intervention	p	Control End	Intervention End
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)
Posterior wall thickness (mm)	8.1 (2)	7.8 (1.1)		8.0 (1.7)	7.6 (1.1)
Change in posterior wall (mm)	-0.2 (1.6)	-0.1 (1.4)	0.89		
LVEDD (mm)	49.7 (5)	49.7 (5)		49.9 (4)	50.1 (4)
Change in LVEDD (mm)	-0.1 (3)	0.08 (4)	0.87		
LVEDS (mm)	30.4 (4)	30.6 (4)		31.3 (4)	31.5 (4)
Change in LVEDS (mm)	0.8 (2.8)	1.1 (4.4)	0.80		
IVS (mm)	8.5 (2)	7.9 (1.6)		8.3 (2)	7.9 (1.9)
Change in IVS (mm)	-0.06 (2)	0.06 (2)	0.10		
Fractional shortening (%)	37.3 (4)	38.9 (7)		36.6 (3)	35.5 (5)
Change in fractional shortening (%)	-2.6 (4.4)	-3.5 (8.2)			

Chapter 9

Quality of Life Change Following Six Months of Exercise Training in Older Normal Individuals

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Quality of Life Change Following Six Months of Exercise Training in Older Normal Individuals

9.1 Introduction

The 1996 United States Surgeon Generals' publication, "Physical Activity and Health," concluded that people of all ages benefit from moderate levels of physical activity. The benefits include reductions in the rates of cardiovascular disease and the maintenance of independent living (138). In addition, exercise is thought to improve mood and health related quality of life, through enhanced psychological well being and improved physical functioning.

Quality of life is difficult to measure objectively and there are a large number of different methods that can be used to do so. Each method has been validated in different age groups or populations (141) and there is no single generally recognised measure of quality of life for older, normal adults. Some questionnaires are more appropriate for healthy or normal populations whilst others are particularly suited to identify degrees of disability. The Medical Outcomes Short Form 36 Item, SF-36, is a widely used and well-validated questionnaire that can be used to assess quality of life in an older population. It is a general outcome measure which attempts to capture aspects of health that are important to all participants (140), in contrast with condition specific measures, which may be criticised for their narrowness. The SF-36 was used to evaluate changes in quality of life between two groups of older, normal individuals. One group underwent six months of exercise training and the other acted as a control group.

9.2 Methods

These have been described in detail in Chapter 3. The SF-36 questionnaire uses eight health scales to measure three aspects of health: - functional status, well being and “overall evaluation of health”. The eight scales measure physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, pain, vitality and general health perception (141). The responses to the questions in each scale are summed to provide eight scores between 0 and 100. A higher score is more positive, i.e. less pain or less limitation. Compliance in the exercise group was assessed by methods detailed in Chapter 3.

9.3 Results

9.3.1 *Number of participants*

The proportion of participants who completed both baseline and end of study questionnaires was far smaller than the total number of subjects included in the trial. Only approximately 55% of the participants completed both baseline and end of study questionnaires but the numbers who did so were similar in the control and the intervention groups. Thus, 16 participants in the intervention and 14 participants in the control group completed both questionnaires.

9.3.2 *Baseline values*

Participants who completed questionnaires scored highly for all aspects of the SF-36 questionnaire, (Table 1, Chapter 9). No significant differences were identified in the baseline SF-36 scores between the intervention and control groups.

9.3.3 *Quality of life changes*

Significantly different changes in quality of life scores were identified between the exercise and the control groups for social functioning but not for any other of the quality of life scores. There was a greater reduction in social functioning in the intervention compared to the control group and within this subgroup, emotional aspects of social functioning reduced significantly more in the intervention group, (Table 2, Chapter 9).

9.3.4 *Compliance*

Overall compliance, (described as percentage of prescribed sessions that were attended) for the intervention group ranged from 0 to 89.9% with a mean value of 59.9%. Reasons for lack of compliance included musculoskeletal injuries and viral illnesses. Five subjects in the intervention group failed to complete six months of exercise training. All of these participants were female and all provided end of study data. Four of the five subjects completed less than one month of training and the fifth trained for three months before illness and social commitments caused her to discontinue training. The mean $\text{VO}_{2\text{max}}$ of these five participants at baseline was 24.8 ml/kg/min and after six months it had fallen to 23.98 ml/kg/min. These subjects had compliance rates of between 0 and 35% but were included in the analysis of all study parameters as the trial data were analysed on an intention to treat basis. Overall compliance for the intervention group excluding these five women was 69.4%. There were 13 men and 19 women in the intervention group. Compliance rates for men who completed more than three months of training were higher than those for the women, 72.2% compared to 66.8%. Compliance rates for all women in the intervention group including those who completed none or very little training was 51.4%.

One subject in the control group significantly increased his weekly physical activity after he admitted that he began training for a half marathon during the trial period. His VO_2max was 44.3 ml/kg/min at baseline and increased to 51.75 ml/kg/min after six months despite being in the control group. These data were also included in the intention to treat analysis. However, after excluding this subject as well as the five non-attendees in the intervention group, the overall study results were unchanged.

9.3.5 *Injuries*

Overall satisfaction with the training program was good. There were four musculoskeletal injuries that were related to the training sessions and all involved either lower back or lower limb pain and were self-limiting. Two ankle injuries occurred during recreational activities that were not part of the training regimen and two of the participants in the intervention group required operations that were also not related to the training program but were associated with a reduction in both compliance and final exercise capacity results.

9.4 Discussion

This study showed that six months of exercise training did not significantly alter overall quality of life scores or physical and mental health perception. Social functioning reduced significantly more in the intervention group but this was not accompanied by any significant improvements in physical functioning.

9.4.1 *Baseline values*

The cohort involved in this study had relatively high scores at the beginning of the trial, i.e. they were relatively healthy, unimpaired, with low pain scores and high

independence at baseline. Thus, they were less likely to change their quality of life significantly over the six month period than a cohort who had low scores to begin with. Other studies have published values for SF-36 scores in both healthy and diseased populations. Scores for the general population in the UK in a paper by Garrett et al were lower than those seen at baseline in our New Zealand cohort (140). Patients with low back pain or varicose veins attending out patient departments also have lower scores than those obtained from our volunteers (141). These baseline scores underline the healthy volunteer cohort that had been recruited, however, scores can vary widely in both healthy and diseased populations. Scores for outpatients with chronic, non-life threatening conditions are not much higher than those seen in a paper, which assessed quality of life in patients undergoing haemodialysis (138). We would have expected our cohort to have lower scores than those cited above because the mean age of subjects in all of the papers noted above were lower than the mean age of the subjects involved in our study.

9.4.2 *Sample size*

Not all participants completed questionnaires at both beginning and end of the study in this trial so that the number of subjects in each group was relatively small. Other studies that have examined quality of life in other populations have had far larger numbers of subjects, which improves the accuracy of the SF-36 in reflecting true, self-perceived health status (140, 141). Pereira et al performed a follow-up telephone interview of 229 postmenopausal women who had been involved in a randomised controlled trial of walking intervention for one year, 10 years previously (196). This showed that women who had been initially assigned to the intervention group ten years previously still maintained significantly higher levels of walking compared to women who had been in the control group. Although there were no significant

differences in self-reported functional ability between the groups at the ten year follow-up, the authors concluded that the numbers may have been too small to detect a change in this relatively young and relatively well population (196). Thus, as our study was much smaller than that reported by Pereira et al it is likely to have been underpowered to identify a change in quality of life resulting from the exercise intervention.

9.4.3 *Assessment of quality of life*

The SF-36 has satisfied rigorous psychometric criteria for internal validity (140) and was thought to be the best available tool to assess quality of life change in our study population. However, no questionnaire accurately reflects quality of life in all individuals and variations also occur due to the method by which the questionnaire is administered to the study population. Clinic based interviews have been shown to systematically exaggerate health status compared with self-assessment, by approximately 12 points using the SF-36 (141). The questionnaires in our study were given to the subjects for them to complete by themselves, with clarification of questions from the principal investigator if necessary. This method of administration would tend to lower the final quality of life scores rather than artificially elevate them (141) and is therefore unlikely to be the cause of the high scores at baseline.

9.4.4 *Changes in quality of life following exercise training*

Most studies examining quality of life have been observational and suggest that regular physical activity and exercise promotion in the elderly lead to improvements in functional status and quality of life (197). Our study identified a significant reduction in social functioning scores in the intervention compared to the control group over the six month period. This unexpected result may have been as a result of

the significant time requirements that were involved in the exercise training program. Subjects in the intervention group were required to attend the exercise training facility three times per week for a six month period. This may have restricted their availability for other social activities, outings and holidays. In comparison, subjects in the control group were able to continue their normal weekly activities following randomisation and thus did not have to alter their social calendars to accommodate the training program. Physical health scores did not however change significantly between the two groups. This lack of change is in contrast to results from one other study (138) that compared changes in quality of life in haemodialysis patients who underwent eight weeks of home-based exercise training followed by eight weeks of in-centre cycling, with haemodialysis patients who served as a control group. A significant improvement in SF36 scores was noted in the intervention group compared to a reduction in the control group over the same time period. The results of this study clearly indicated that physical activity was specific in affecting the physical aspects of health-related quality of life because there were no changes in the mental health scores in either group of patients (138).

Other authors have concluded that the elderly may derive substantial improvements in mental as well as physical health by participation in an exercise regimen (63). A randomised controlled trial in older, healthy volunteers aged 61 to 80 years showed significantly better life satisfaction, perceived health status and maximal physical exertion in a group undergoing 32 weeks of exercise classes compared to a group who received health education alone (198). Thus, aerobic exercise classes were demonstrated not only to be acceptable and effective in this age group but were also significantly better in respect to perceived health status than health education. Our 24

week study did not show such improvements but may have been too short to affect quality of life significantly.

9.4.5 *Other studies assessing the changes in quality of life following exercise training*

Lavie et al assessed quality of life in over 100 obese and non-obese patients with coronary artery disease using the SF-36 questionnaire before and after a three month exercise rehabilitation programme (199). A significant improvement in quality of life following cardiac rehabilitation was identified in this retrospective analysis in both non-obese as well as obese patients. The lack of change in quality of life seen in our study may be due to the high scores seen at baseline in our cohort compared to those obtained from a diseased population. Health education was used in another randomised controlled trial in older, healthy, community living adults that aimed to promote increased walking over a one year period. A positive effect of this intervention was noted on self-related health, frequency of social contact and walking behaviour (200), but these changes were not assessed using the SF36 questionnaire. These effects were however, thought to have the potential to reduce mortality by 22% if increased activity was maintained for five years.

9.4.6 *Compliance*

Overall compliance with the exercise training program was 69.4%, excluding those subjects who did not attend more than three months of training sessions. This value is slightly lower than other training programs that have included very small numbers of participants (90), but is comparable with larger studies in the elderly, which report values of between 60 and 80% attendance (155, 201). Many studies do not report compliance figures at all; although other studies have shown that home based

training regimens achieve higher compliance rates than those that require attendance at a training facility. Compliance is an important factor when designing any training program and motivation remains a challenge for cardiovascular preventative programs (91). Lack of sufficient time to attend the training sessions was the main reason for non-attendance in our highly motivated volunteers and this is in agreement with other studies that have discussed compliance in supervised exercise training programs. We were unable to provide exercise training sessions at all times of the day and every day of the week and this may have limited attendance in those for whom the training times were less convenient. Although we were able to provide some financial compensation to the subjects in the form of petrol vouchers, the lack of adequate and affordable public transport to the training facility also reduced compliance rates, especially for those participants without access to a private car. Any successful training program must optimise training facilities in order to achieve the greatest rates of attendance and this should include improvements in access, training facilities with good transport links and car parking and financial incentives or compensation for the volunteer participants. Maximal adherence to an activity program is facilitated by choosing activities that are interesting and enjoyable with the possibility of developing group and social interactions (57). These factors were highlighted in a study that compared the health benefits of playing three rounds of golf per week for 20 weeks in a randomised controlled trial (95). Compliance rates were extremely good with only two out of 55 participants in each arm failing to complete the study.

The intention to exercise depends upon personal attitudes as well as social norms (202). The social norm that old age is a time to slow down and take a rest must be corrected. However, as there is a very small margin between an effective and a

dangerous exercise prescription in the very elderly, compliance will be improved if exercise is appropriately prescribed and supervised (202).

9.4.7 *Gender differences*

In our study, women had significantly lower attendance rates at exercise training sessions than men, but this finding has not been described in other studies. Both Spina and Kohrt report similar frequency, duration and intensities of exercise training in older men and women over a period of nine months (62, 90). Exercise training has traditionally been more popular amongst men than women and this is the most likely explanation for the difference in compliance rates between the genders.

9.4.8 *Injuries*

In our study, only three subjects incurred injuries that resulted in a cessation or modification of exercise for more than one week. In a similar study, 60% of the participants who completed the training regimen experienced painful episodes relating to the lower limbs that limited their ability to exercise for up to one week (155). We felt that the low incidence of injuries in our study was due to both effective and appropriate prescribing that was individualised to each participants initial level of fitness (202), as well as to the compulsory warm up and warm down period during each session.

9.5 *Conclusions*

- The results of our trial do not provide additional data to support improved quality of life following six months of exercise training in older, healthy individuals. However, these results should be assessed with caution, as they are most likely to represent a type two error than a real negative effect.

- This exercise program was acceptable to older people, resulted in substantial improvements in exercise capacity and did not cause large numbers of injuries.

Table 1 Chapter 9
Baseline SF-36 scores

SF-36 Category	Score
(0-100)	Mean (SD)
General health perceptions	89 (11)
Physical functioning	88 (17)
Social functioning	94 (14)
Pain index	85 (14)
Role limitations due to physical problems	93 (17)
Role limitations due to emotional problems	90 (22)
Vitality (energy and fatigue)	75 (10)
Mental health index	83 (12)

Table 2 Chapter 9

Quality of life change

	Control Mean(SD)	Intervention Mean(SD)	p	Control End Mean(SD)	Intervention End Mean(SD)	p
Social functioning	92.2 (16)	94.7 (13)	0.6	91 (21)	91 (17)	0.9
Change in social functioning	5 (14)	-7 (18)	0.04*			
Emotional health (social functioning)	9.4 (1.3)	9.6 (1)	0.6	9.3 (1.7)	9.3 (1.4)	0.9
Change in emotional health (social functioning)	-0.18 (1.8)	-0.6 (1.4)	0.04*			
General health	88 (10)	90 (11)	0.61	85 (24)	85 (20)	0.9
Change in general health	-1.1 (22)	-4.2 (20)	0.7			
Vitality	74 (8)	76 (12)	0.7	72 (20)	76 (13)	0.3
Change in vitality	2.8 (13)	3.6 (14)	0.87			

*** = p<0.05**

Table 3 Chapter 9

Quality of life comparisons to other studies

SF-36 Category (0-100)	Oxenham Mean (SD)	Garrett Mean (SD)	Lyons Mean (SD)	Painter Mean (SD)
General health perceptions	89 (11)	69	55	45 (20)
Physical functioning	88 (17)	79	60	50 (24)
Social functioning	94 (14)	79	62	75 (25)
Pain index	85 (14)	77	56	70 (26)
Role limitations due to physical problems	93 (17)	77	41	63 (44)
Role limitations due to emotional problems	90 (22)	75	68	73 (42)
Vitality (energy and fatigue)	75 (10)	61	46	45 (26)
Mental health index	83 (12)	74	71	74 (17)

(138, 140, 141)

Chapter 10

Discussion

Are Age-Related Changes in Cardiovascular Function Modifiable Using Exercise Training?

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Are Age-Related Changes in Cardiovascular Function Modifiable Using Exercise Training?

10.1 Increasing age is associated with changes in diastolic function

Aging results in significant changes in diastolic function, which have traditionally been identified using Doppler transmitral flow velocities. These reveal a reduction and prolongation of early diastolic left ventricular filling and a relative increase in left ventricular filling during late diastole (29). More recently, mitral annular diastolic velocities have been shown to fall with increasing age, suggesting reduced or slowed diastolic longitudinal movement of the mitral annulus (32, 35). The cause of these observations is thought to be a “stiffening” of the left ventricle with advancing age, but direct measurement of left ventricular compliance is not possible in humans. MRI with tagging allows direct measurement of left ventricular motion and strain because it enables us to plot the movement of hundreds of points fixed with respect to the left ventricular myocardium. Whilst not measuring compliance, it does provide information about what is happening within the myocardium and unlike tissue Doppler imaging the information obtained refers to three dimensional myocardial motion rather than movement in only one plane. MRI with tagging has been able to show that, in young people there is a rapid untwisting and dilatation of the left ventricle during myocardial relaxation and early diastole (100). This movement is thought to be responsible for the negative intraventricular pressure created in the left ventricular cavity just before mitral inflow, which results in suction of blood across the mitral valve (203). If untwisting and dilatation of the left ventricle were delayed or incomplete, there would be a reduction or loss of the suction effect in the left ventricular cavity and thus a reduction in the velocity of

blood flowing across the mitral valve during early diastole. MRI with tagging confirms delayed and incomplete myocardial relaxation during early diastole in older compared to younger people (20) and provides a mechanism to explain the reduced early diastolic transmitral flow seen in older people. We did not measure intracavity pressures or transmitral flow velocities during magnetic resonance scanning, so a direct association between alterations in three-dimensional strain and reduced early left ventricular filling during early diastole cannot be proven.

Changes in the morphology of the left ventricle do not explain the differences in relaxation rates or strain between young and old normal adults during diastole. Data from a group of young volunteers in whom increased left ventricular mass was present due to previously corrected coarctation of the aorta did not differ from that obtained from the young normal group in Chapter 2 with respect to strain during early diastole, (personal communication AA Young). Therefore, we propose that the changes described in older people during myocardial relaxation and diastole do result in a reduction in early left ventricular filling in older normal adults and that they are likely to be due to the result of the aging process.

10.2 What is the significance of age-related changes in diastolic function?

The significance of altered diastolic function with respect to the ability of older people to live normally has not been clarified, but some indices of diastolic function have been directly related to a reduction in exercise capacity in older people (51). We were not able to identify any significant correlation between exercise capacity and any echocardiographic measure of diastolic function, including tissue Doppler imaging measurements in our group of older volunteers in the exercise training

study. This lack of correlation may have been due to the homogeneity of our study population with respect to diastolic function and its relatively narrow age-range, (Graphs 1 and 2, Chapter 5). However, the lack of correlation between VO_2max and markers of diastolic function such as E' , which change in a linear fashion with respect to the severity of diastolic dysfunction (118), suggest that diastolic function is not strongly correlated to exercise capacity despite previous reports suggesting this to be the case (51).

The relationships between diastolic change and the subsequent development of heart failure in older people are also unknown (152). Heart failure is particularly prevalent in older people and in this age group, often presents with minimal reduction in left ventricular systolic function (204). It is not known whether age-related changes in diastolic function cause or contribute to this “diastolic” heart failure but some large-scale prospective trials are currently underway that will address this issue (205). If a change in diastolic function does predispose or cause heart failure in the elderly then restoration of more “youthful” diastolic function could reduce the incidence of this costly disease. However, although it would seem reasonable to assume that interventions that could return diastolic function to “normal” would be advantageous in terms of daily functioning as well as prognosis, it is not known how or if diastolic function can be altered or whether exercise training can be used to affect favourable change in diastolic function in older people.

10.3 Diastolic function in athletes

Many studies suggest that master athletes have “improved” or more “youthful” (165), diastolic function than their age-matched sedentary peers (78,82). However, in all of these studies significant differences in heart rates between athletes and the

control participants could have accounted for the higher E/A ratios described in athletes. Takemoto et al suggest that diastolic abnormalities associated with aging are less marked in athletes, in whom they could find no correlation between E/A ratio and age (83). Some studies have shown no differences between E/A ratios in athletes and sedentary peers (80, 150, 186), but on the whole, E/A ratios do tend to be higher in fitter individuals than in the general population. Perhaps a reduction in E/A ratios with age simply reflects the presence of underlying coronary artery disease in sedentary individuals that is not present in athletes? However, despite the presence of perfusion defects in four of ten athletes, one study was still able to show that E/A ratios were higher in ten master athletes compared to sedentary peers (80). Thus, at least some of the reported age-related alterations in diastolic function could be the consequence of a sedentary lifestyle.

Tissue Doppler imaging measurements are less dependent on heart rate and blood flow (39, 115) and assess functional and structural myocardial status by measuring myocardial velocities (128). They should therefore be able to identify whether athletes display smaller degrees of slowing or stiffening of myocardial movement than their sedentary peers, or whether the differences are in fact due simply to differences in heart rate. Palka et al showed a 42% increase in myocardial velocity gradients in early diastole in athletes compared to sedentary peers and this finding was independent of heart rate (85). A similar study showed values for E' to be 25% higher than those seen in sedentary older men (154) and supports the assumption that diastolic function is more “youthful” in master athletes than in the sedentary, normal aging population.

10.4 Can diastolic function be changed with exercise training?

If master athletes have more “youthful” diastolic function, then perhaps exercise training could result in a rejuvenation of diastolic function in older, previously sedentary adults? The results of our randomised controlled trial of exercise training in older normal adults show that six months of exercise training are insufficient to alter diastolic function significantly. These results are in contrast to those from animal studies (36) and non-randomised trials (70,73), which suggest that diastolic function can be altered by exercise training. There are several possible reasons for the lack of observed effect in our study.

10.4.1 Type two error (underpowered study)

Current literature regarding the effects of exercise in humans predicted some of the changes seen following exercise training in the intervention group (130, 181). However, although these findings were expected, the changes seen in the intervention group were not large enough to be significantly different from those seen in the control group. For example, an expected response to exercise training, based on previous studies of exercise training would predict that heart rate would slow (55), blood pressure and cholesterol levels would fall (47), arterial compliance would increase (137) and body fat levels would reduce (182). All of these effects were observed, but not in amounts significantly different from those identified in the control group. Parameters of diastolic function also changed in the expected direction, but only by small amounts. In view of these trends towards positive change in many of the variables that were measured, the most likely explanation for the lack of significant observed effect on cardiovascular function and in particular, diastolic function in our trial was that it was too small or too short to show a difference in this

population, i.e. there was a type two error. Causes of type two errors in this study will be discussed further.

The study population was too normal to begin with

It is easier to change an abnormal parameter than to lower one that is only marginally raised to start with. This is a likely explanation for the negative outcome in this exercise training study. Although age-related changes in Doppler indices of diastolic function were observed in our older normal volunteers at baseline, values for E/A were not as low as those described in other studies (206). In hindsight it may have been appropriate to include significantly altered diastolic function as an inclusion criterion for the study participants. We did not do this because of the belief, based on published reports, that the majority of our study population should have significant reductions in E/A ratios (27), as well as low E' velocities (32), because of the age range chosen.

One study that examined normal subjects between the ages of 70 and 87 years showed that 87% had E/A ratios that were less than 1.0 (27). An even older population than that included in our study would have been likely to have more abnormal diastolic function to start with, thus avoiding a type two error. However, although the upper age limit for inclusion into our trial was 85 years of age, few octogenarians volunteered for the study and most of those who did had significant coexisting diseases or orthopaedic problems and had to be excluded during screening. Thus, it would have been difficult to recruit volunteers significantly older than those who were included.

It has been suggested that the majority of the population above the age of 65 years have significantly altered diastolic function (29), but diastolic abnormalities may be less marked in subjects who are relatively fit, as well as in those who have been vigorously screened to exclude significant cardiac disease and hypertension. The Framingham study and other large studies that have described diastolic function in older people did not screen all participants to identify undisclosed cardiac problems using stress testing routinely (23). Mantero et al measured Doppler transmitral flow velocities in older people who were normal but had not undergone formal stress testing to exclude cardiac disease. They showed mean E/A ratios of 0.9 ± 0.2 in the age range 60 to 70 years and mean E/A ratios of 0.7 ± 0.2 in the age range 70 to 85 years (207). These values are slightly lower than mean values for E/A of 0.9 ± 0.2 , in our trial participants, whose average age was 67 years old. Thus, the diastolic abnormalities described to be present in the majority of adults over the age of 65 years may in fact be the result of undiagnosed cardiovascular disease or they may be due to minor, early coronary artery disease affecting the microvasculature that formal screening tests fail to identify. A recent study that examined the prevalence of diastolic abnormalities in the community showed that although diastolic abnormalities become more common with advancing age, only 15.8% of people over the age of 50 years have diastolic dysfunction defined by the European Working Group on Heart Failure (208). Moreover, when adults with hypertension, diabetes or known coronary artery disease are excluded, this prevalence falls to 4.6% (161). Therefore, the assumption that diastolic function changes with increasing age may be similar to the assumption that age is associated with hypertension and left ventricular hypertrophy; a fact that when examining primitive populations or groups that have been carefully screened to exclude coexisting disease does not hold true.

The assumption that diastolic abnormalities accompany increasing age and are not due to undiagnosed disease is however, supported by a study that examined ten old and ten young men, all of whom underwent extensive screening to exclude important cardiovascular disease (22). This study measured invasive haemodynamic and radionuclide parameters as well as Doppler transmitral flow velocities and concluded that the changes in transmitral flow that are associated with aging are likely to be due to an intrinsic aging effect rather than the result of subclinical cardiac disease. It is interesting to note that in this group of older normal men, four of whom undertook regular exercise, the mean E/A ratio was 0.95, i.e. greater than values quoted in other studies (26), but similar to the mean values for subjects in our study.

The European Working group definition of abnormal diastolic function states that the E/A ratio can fall to as low as 0.5 in people over the age of 50 years and still remain within the age-matched normal range (208). Thus, whilst significant changes in transmitral flow velocities may be present in older persons, they are not defined as an abnormality by these criteria. However, although the prevalence of diastolic abnormalities may be lower in older screened populations than was originally thought, some degree of altered diastolic function is likely to be attributable to advancing age rather than coexisting disease and the permanence and mutability of these changes remains unclear (161).

Choice of study population

It was the aim of our study to examine the permanence and mutability of age-related changes in diastolic function rather than changes seen as a consequence of a disease. The reason for studying normal individuals rather than, for example, a hypertensive population was the fact that diastolic function is affected by a multitude of

haemodynamic factors. Each drug that is used to treat hypertension can also alter diastolic function by changing loading conditions or heart rate. Thus, in a hypertensive population, doses and types of drugs would have had to be kept constant during the trial period and particularly on days when measurements were taken. In addition, structural changes in the heart that occur as a result of hypertension or resolve as a result of treatment would also have to be taken into consideration when assessing a change in diastolic function. Whilst a diseased population may have greater potential to change, any observed effect could be difficult to attribute to the intervention itself rather than to treatment received during or prior to the training program. In addition, there have been very few exercise training studies that have concentrated on individuals over the age of 60 years, or that have included female participants. Thus, it was felt that a study examining the normal older population in a randomised controlled trial would provide novel and useful information regardless of the final trial conclusions.

Non-homogeneous study population

A homogeneous study population reduces individual variation with respect to the response to an intervention and potentially also reduces the chance of type two errors. Left ventricular hypertrophy is more common in older women athletes compared to male athletes (157) and it has been postulated that there are significant gender differences in the responses of the cardiovascular system to exercise training (54). However, despite potentially introducing confounding factors regarding gender specific responses to training, we decided to recruit both men and women into the study so that it improved the general applicability of the trial results to the older population where women make up more than 50% of all age groups above 65 years old. When our trial data were analysed separately for men and women, no differences

were seen in the responses of each gender to exercise training. The only gender difference that we did observe was in compliance rates in the intervention group where all non-attendees were female. This may have many causes but might be the reason for the paucity of exercise training data currently available in older women.

Intention to treat analysis

The trial was analysed on an intention to treat basis in order to avoid the introduction of observer bias. Thus, subjects who failed to complete the exercise-training program, as well as those in the control group who had increased their activity levels were included in the analysis. This makes the chance of a type two error higher but it also makes the scientific conclusions that result from the study more robust and generalisable (209). There was a 16% drop out rate in the exercise group, which effectively reduced the sample size. These non-attenders showed no improvement in fitness parameters and their inclusion into the analysis would tend to underestimate the effect of exercise training on the measured variables. However, when the trial results were analysed after all non-compliant participants had been excluded, the overall results were unchanged.

Choice of end points

E' and E/E' were chosen as primary endpoints because of previous evidence that suggested that these markers were the most accurate estimates of diastolic function (122, 163). Reports published since completion of our study cast doubt on the usefulness of E' as a measure of diastolic function if this is measured from the basal septum or mitral annulus (154). Caso et al showed that E' was not significantly higher in young athletes compared to sedentary controls when it was measured in the basal septum. However, when E' was measured in the inferior segment of the left

ventricle, it was significantly higher in young athletes (154). This study did not examine older athletes and so cannot be directly referable to our study population, but it does cast some doubt upon the usefulness of E' from the basal septum or mitral annulus as a way of identifying any change as a result of exercise training.

Changes in diastolic function that are likely to be the result of exercise training are small

When designing the study, new echocardiographic parameters were chosen as primary endpoints so that changes in these parameters could identify a true change in diastolic function rather than differences resulting from altered haemodynamics. However, at the time of study design there were few published reports using these parameters and no exercise training studies that had incorporated them. As a result, the expected changes in E' or E/E' following exercise training were not known and may have been overestimated. The study had adequate power, (80% at the five percent significance level) to detect a difference of 1.3 or 16% of baseline E/E' between the groups. If you considered a clinically relevant difference between groups to be of this order then the study was adequately powered, but if you considered smaller differences in E/E' between groups to be clinically relevant then the study may have been underpowered. Palka et al reported a 42% difference in tissue Doppler myocardial velocity gradients in the posterior left ventricular wall of athletes compared to controls and so we felt that a 16% difference in E/E' could be attainable with exercise training. Taking the primary outcome variable: the change in E/E' and comparing the difference observed between those randomised to exercise and those randomised to control, (mean 0.17 SD1.81), two groups of 1,861 would be required for this study to reach statistical significance. In order to show a significant

difference in E/A ratio of 0.014 (SD 0.2), two groups of 3205 people randomised to intervention and control would have been needed.

10.4.1 *Other reasons for negative trial outcome*

Compliance in the control group

If the control group became fitter over the trial period then any change seen in the intervention group would need to be even larger to reach significance. Volunteers for this study may have been attracted to it by the possibility of becoming involved in an exercise training program. Thus, despite having been asked to maintain their baseline levels of activity, some subjects in the control group may have increased their activity levels and their fitness over the trial period. This could result in small improvements in fitness in the control group and could be the cause of some of the changes seen in variables such as heart rate in this group over the study period. There was no overall increase in VO_2max in the control group but it must be taken into consideration that this measurement was unblinded and therefore could have been influenced by the technicians' belief that exercise capacity in individuals from the control group should not have changed over the six month period. In order to overcome this potential bias, the baseline VO_2max results were not available at the time of the end of study tests. In addition, strict criteria were applied to define maximal values for exercise capacity. Despite these precautions, measuring maximal exercise capacity is known to be a relatively inaccurate technique and it is therefore feasible that improvements in fitness in the control group were not identified because the VO_2max tests were unblinded.

Physical activity questionnaires were administered at baseline and end of study to all the participants and these did not reveal any increase in activity levels in the control

group. However, the participants themselves completed these questionnaires and there were obvious flaws in their accuracy regarding actual activity levels.

Podometers are probably the most accurate way of measuring daily activity levels but these were not available to us at the time the study was performed.

Inadequate training regimen

The exercise training regimen achieved significant improvements in exercise capacity which were similar in magnitude to other exercise training studies in older people, (Table 4, Chapter 3). It is possible, however that the training regimen was not adequate enough to affect diastolic function. Several other exercise training studies have concluded that the duration and intensity of exercise training that is required to significantly improve exercise capacity is different from that required to change cardiovascular function, lipid profile or body composition, (170, 197, 210). If our study were compared to studies that have published positive results, then it would be difficult to conclude that the training protocol used in our study was not intense enough because these other studies have used training protocols that were less intense (70, 153). However, as significant reductions in the expected age-related changes in diastolic function have been documented in master athletes (85, 154), it is possible that the reason for the lack of effect in our study was that the exercise training stimulus was not continued for long enough. We did not have the resources to continue the training regimen for longer than six months, but it would have been interesting to continue the study for at least one year. However, one study did continue exercise training for twelve months and was unable to report significant change in cardiovascular function as a result, despite large increases in exercise capacity in the participants (90).

Changes in diastolic function did not correlate with changes in exercise capacity in our study, despite some participants making large increases in fitness. Thus, either measurements of exercise capacity were inaccurate or short term improvements in fitness do not cause, (or result from) altered diastolic function (167). Thus, the reason for improved diastolic function in observational studies of master athletes (85, 164) may be less to do with exercise training and more to do with a genetic predisposition to alterations in cardiac function as a result of exercise, which cause the individual to continue to train into old age.

Evidence from previous trials is inaccurate or misleading

The fact that the study was a randomised controlled trial may have reduced the chance of identifying significant differences as a result of exercise training. Whilst the results of this trial potentially disprove existing evidence regarding the changes in diastolic function that can occur following exercise training (70, 73), it must be stressed that this trial was a randomised controlled trial that had strict blinding with respect to data measurement and analysis. This trial therefore adds important, robust evidence to current literature, almost all of which has come from non-randomised or non-controlled trials in which blinding methods during measurement and analysis of data are not described. These factors should be considered when examining the current evidence and accepted conclusions regarding the possible benefits of exercise in older people. Perhaps the previous studies that have reported changes to diastolic function following training have been influenced by changes in heart rate and loading conditions? This is likely to be the case for studies reporting changes in diastolic function secondary to drugs such as verapamil (69). We are currently unaware of other studies that have examined the effects of exercise training on diastolic function using newer, less haemodynamically dependent measures such as

tissue Doppler imaging. Based on our trial results we would suggest that further, well-designed, large trials to re-examine this question are required before it can be concluded that exercise training is unable to change diastolic function in older normal individuals.

Exercise training does not alter central cardiovascular function

The hypothesis that exercise training may change diastolic function is based partly on evidence that suggests that exercise training alters central cardiovascular function (169). However, several authors describe significant changes in peripheral circulatory and skeletal muscle function rather than central cardiovascular function in previously sedentary individuals following exercise training (84). Ogawa et al compared sedentary old and young men and women with trained, age-matched adults and found that age-related reductions in peripheral oxygen extraction were attenuated in trained individuals (54). In addition, skeletal muscle oxidative capacity and capillary density were lower in older compared to young sedentary people but not in older versus young trained individuals suggesting that exercise training has a significant affect on skeletal muscle function (169). Although there was no significant correlation between diastolic indices and exercise capacity in our study population, the fact that exercise capacity did correlate significantly with fat free mass suggests that peripheral factors such as muscle mass and function play an important role in accounting for exercise capacity in older people (211). These findings suggest that a significant peripheral component is responsible for training related improvements in exercise capacity and that diastolic function is less important at limiting exercise capacity than has been reported by previous authors (51). Our group have also shown that the lower VO_2max seen in type 2 diabetics is due largely to a lower peripheral arteriovenous oxygen difference and not as a result

of differences in diastolic function or other indices of central cardiovascular function seen in diabetics compared to normal age and body mass index-matched adults (184). This data would also concur with the study by Fleg et al that suggested that the reduction in VO_2max with increasing age was due to a reduction in muscle mass (53). Thus, exercise training may not have resulted in significant changes in diastolic function in our study because this intervention primarily affects peripheral circulatory and skeletal muscle function rather than central cardiovascular function.

10.4.3 *Role of age and mutability of the left ventricle*

Studies involving young adults reveal significant changes in left ventricular structure following exercise training, whilst similar trials in older men fail to identify significant alterations to left ventricular shape or structure (82, 157, 194). This evidence suggests therefore, that with advancing age there is a loss or limitation of the degree to which a non-diseased left ventricle will remodel as a response to exercise training. Although exercise capacity can improve in older populations to the same extent as in younger groups (47), the ability of myocardial structure and function to change in response to exercise training appears to be lost with advancing age (15). If this is the case, then diastolic function is unlikely to change following exercise training except as a result of changes in blood volume, heart rate and blood pressure but not as a result of material or molecular modification in the myocardium.

10.5 *Advantages and disadvantages of performing an exercise training study in older people*

Older, normal volunteers are generally enthusiastic, punctual and committed participants in any trial. They tend to have larger amounts of free time to attend training sessions and appointments than younger people who may be in full time

employment or have caring duties. In our experience, they are also interested in the aging process, how to delay it and what the causes of aging are. They are therefore easy to recruit and very amenable to whatever requirements are asked of them during the study.

Screening to identify normal older individuals is more likely to result in exclusions the greater the age of the participants. In our experience, few volunteers over the age of 80 years were able to successfully complete the screening procedure. In this respect, training studies that include the “young old” are likely to be easier to perform but are more likely to show no effect because of smaller age-associated abnormalities in cardiovascular function.

Older people are however, less likely to feel able to exercise and push themselves physically because of social stereotypes that suggest that the “third age” is a time in which to relax and take things easy, or because of a fear of injury. This was the case for many of the female participants in our study and in this respect a supervised setting for the exercise training provides reassurance, a sense of safety and encourages maximum effort from the volunteers. Injury and a worsening of pre-existing orthopaedic problems was not a significant issue in this trial, despite the age and prior concerns of the participants.

10.6 How would we design the study differently in the future?

Future studies of exercise training in older normal individuals should probably be continued for a longer period of time than six months in order to have the best possible chance of identifying change. Incentives to improve access to training such as exercise training sessions on every day of the week or during the evening would

improve attendance as would financial assistance to pay for transport costs to the training facility. Compliance within the control group is an issue that is difficult to overcome. We advertised for this study carefully, so that all volunteers would not expect to undergo some form of exercise training, but the volunteers were nevertheless interested in the possibility of attending a free, supervised exercise training session and most, but not all of the subjects randomised to the control group expressed their disappointment at being allocated to this group. In order to overcome this disappointment, as well as to encourage an adherence to baseline fitness levels, it would have been useful to have been able to provide an exercise training program for the control group, either as a crossover design, or sequential to the initial phase of the study, as an incentive for participants to delay any planned personal exercise training regimen. This was unfortunately not possible and so an increase in activity levels in the control group is one of the most likely causes for both the negative outcome of the study but also some of the changes in measured parameters seen in this group over the trial period.

10.7 Conclusions

- Changes in myocardial strain can be identified in older compared to young normal people using MRI with tagging. These changes identify a prolongation of myocardial relaxation with incomplete ventricular dilatation during early diastole. They are likely to result in a reduction and slowing of left ventricular filling during early diastole and are thought to be due to the aging process.
- Significant changes in diastolic function in older people may be less marked in a group of volunteers that have been screened rigorously to exclude coexisting cardiovascular disease than in the general, older population.

- Exercise training in older normal people is safe and can produce significant improvements in exercise capacity over a six month period.
- Reductions in blood pressure, resting heart rate and arterial stiffness occur as a result of exercise training but significantly greater reductions than in the control group could not be identified conclusively in our study, which may have been underpowered to identify these differences.
- Diastolic function is not appreciably affected by a six month exercise training regimen when measured using both tissue Doppler as well as transmitral flow velocities. This may be because significant changes to cardiovascular structure and function are not possible in older adults following exercise training or because changes in diastolic function due to exercise training were too small to be identified in this trial.
- Trends towards favourable changes in diastolic function were seen, but longer and larger studies are needed to prove conclusively whether diastolic function can be altered using exercise training in older normal people.
- Significant reductions in serum triglyceride concentrations were seen as a result of six months of endurance exercise training in older normal people.
- Trends towards an increase in HDL cholesterol and other improvements in lipid profile were seen but are likely to be small in a normal, older population as a result of exercise training and significant increases could not be proven in this study.
- Although a trend towards increased fat free mass with exercise training was seen, significant reductions in body weight or body fat were not observed as a response to exercise training for six months without a change in dietary intake. It is likely that exercise training alone is more effective at preventing weight gain than as a way to promote weight loss.

- Maximal exercise capacity correlates more closely with fat free mass than with measures of diastolic function.
- Physiological left ventricular hypertrophy was not identified in the subjects as a response to exercise training and neither were significant changes in cardiac chamber size. This may be due to a loss of the ability of the heart to adapt to the exercise training stimulus in older age.
- Significant improvements in quality of life were not identified in a population that had a good quality of life at the beginning of the trial.
- No significant differences were identified between the responses of male and female participants to exercise training except that compliance with exercise training was lower in women than in men.
- The results of this study add important evidence to current literature regarding the response of cardiovascular function to exercise training in older people because, unlike most other studies it was a randomised controlled trial with strict blinding with respect to most of the measurements that were taken.

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Exercise Training for Older People

Are you older than 65 ?

Do you take little regular exercise?

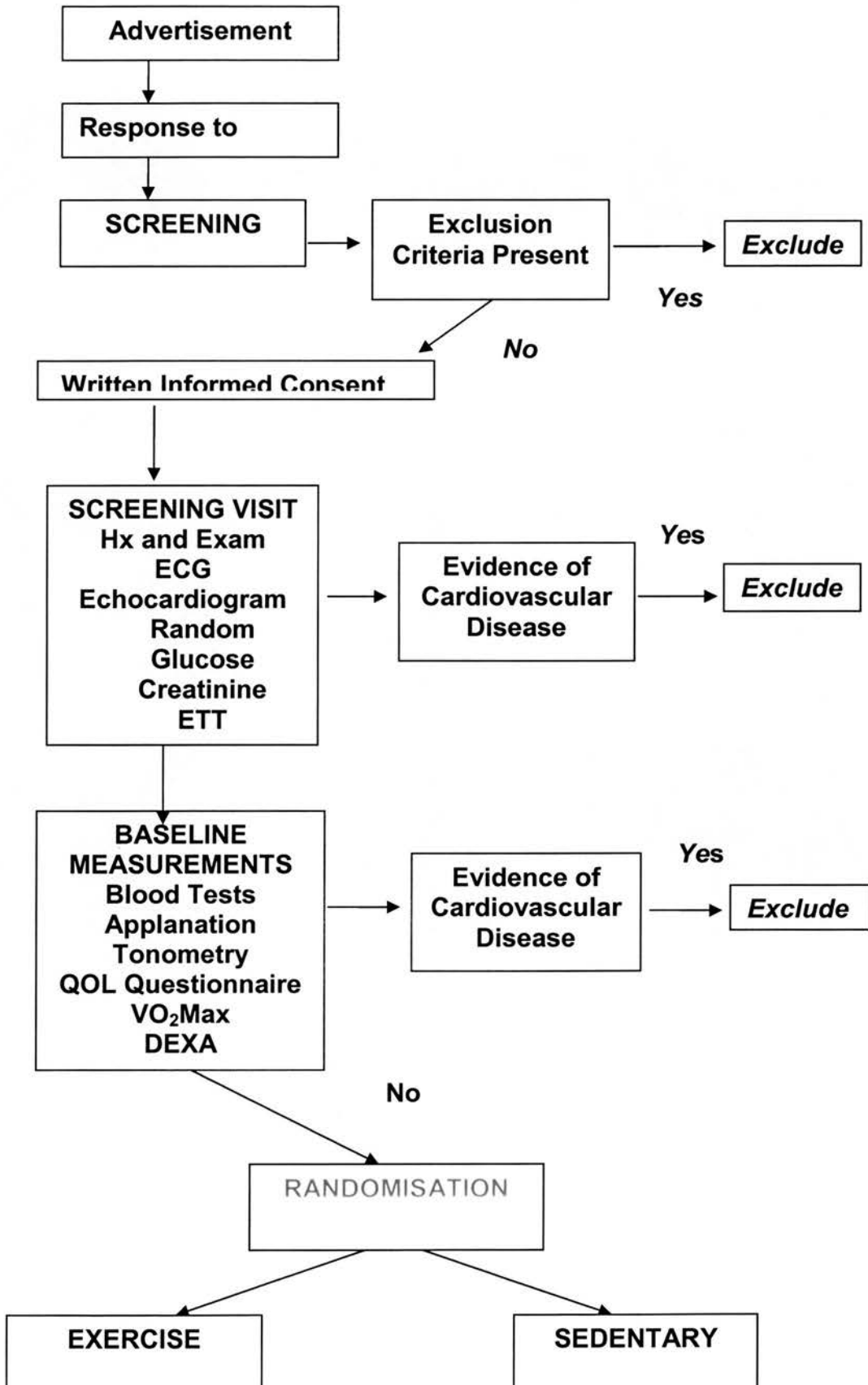
The Departments of Medicine and Sport and
Exercise Science at the University of Auckland
are studying the effects of exercise on the heart.
We are looking for men and women who have no
previous heart problems and would be interested
in taking part in our study.

please phone:

(9) 307 4949 extn 7654 or 7668

Appendix 2

Flow diagram



Appendix 3

Physical activity scoring

METS levels for each activity on the Nurses Health Questionnaire

Walk	Casual	2.5 MET
	Average	3.0 MET
	Brisk	4.0 MET
	Very Brisk	4.5 MET
Jog (< 10 min / mile)		7.0 MET
Run (> 10 min / mile)		12 MET
Bicycle		7.0 MET
Callisthenics		6.0 MET
Tennis/Squash		7.0 MET
Swimming		7.0 MET
Other Aerobic Recreation		4.5 MET

(142)